



# Endocrinology

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## PROGRESSIVE LIPODYSTROPHY AND HYPERTHYROIDISM

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The disease, or rather syndrome, which Simons called "Progressive lipodystrophy" is certainly not a new discovery. Zalla (1), for example, quotes the oldest case known described by Morgagni. A short time back, when reading the clinical histories of girls given to masturbation, by Zambaco (2), we found the indication, made in passing, that one of them had "a great lack of fat on the upper half of the body, as compared with the lower half." And it is probable that more data, both literary and iconographical, can be found dealing with this question. But the first to make an accurate description of the syndrome was Barraquer (3), of Barcelona, in 1907. His case was that of a girl of 16, whose face began to grow thin in such a fashion from the time she was 12, that she decided to consult our distinguished countryman, who found a very intense fusion of the adipose tissues over the upper part of her body, whilst the lower part contained a normal amount of fat. This author insisted on the complete normality of the skin and of the muscular tissues and suggested a probable intervention of the vegetative nervous system in its pathogeny. His description was thus complete and his case one of the most typical described (Fig. 1).

We draw attention to this to suggest once again that this syndrome should be known as the "Syndrome of Barraquer-Simons," as Simons, although he added interesting anatomic and pathologic data in his reports published in 1911 and 1913 (4), found no need to alter, clinically or pathogenically, the fundamental lines of the first description by Barraquer.

After the publication of Barraquer and before those of Simons appeared cases by Campbell (1907) (5) and Pic and Gardere (1909) (6), and many more at a later date, so that at present we have knowledge of more than 60, which we will not mention especially as it is not our object to make a bibliographical review, which can be found in the monographs of Boissonnais (7), Long and Bickel (8), Weber (9) and Smith (10). In Spain contributions have been made to the causation of this disease by Marañon (11), Pardo (12) and, more recently, Barraquer (13).

In view of several cases which we have seen recently we wish to add data to those already known as to the symptomatology and pathogeny of progressive lipodystrophy.

In the first place, it appears that the name by which this syndrome is usually known is quite improper. Barraquer (3) called it "Atrophy of the cellulo-adipose tissues"; Simons (4) called it "Progressive lipodystrophy," which has been universally accepted. However, both of these names are notably improper, since neither expresses the real characteristic of the process, which is its strange localization. In his latest work, Barraquer (13) calls it "Juvenile adipose dystrophy," which is also much too vague. Probably the most accurate name would be "Cephalo-thoracic lipodystrophia," which indicates the really pathognomonic character of the process, that is to say, its localization in the upper part of the body. However, we do not propose to enter into discussion over the name, still less so in a syndrome whose pathogeny is still imperfectly known.

Since we have devoted special attention to the study of this syndrome, we have been able to observe that it is not a rare disease, but on the contrary is rather frequent although, as usual in all diseases, the extreme cases are seldom met with. But with respect to the distribution of the fat (leaving aside those cases in which this distribution is uniform and normal),

we notice two kinds of imbalance: the first, which is the case of those people whose fat accumulates chiefly in the upper part



Fig 1 The first case of lipodystrophy described by Barraquer

of the body, what we might call typical "physiological" fatness, which comes over heavy eaters and drinkers whose volume increases at the neck, chest and upper part of the belly (plethoric

type) and whose legs remain slender; and the other kind in which the fatness affects chiefly the lower part of the body. The latter is so frequent that they form a class apart from normal beings only in their aesthetic aspect. They are nearly always women, frequently young people with no apparent connection with an outward cause. At any rate, in our Southern countries this is so common that there is a popular saying that these women have "the beauty of the thrush, a thin face on a fat body,"\* which is a description, even in its translated form, which corresponds to the primitive description of progressive lipodystrophy.

As we have said, when the distribution of the adipose pannicle is carefully observed in his patients, one is surprised to see the large proportion which present the cervical-thoracic lipodystrophy, either in an advanced state or in lesser degrees, which are really "frustrated forms" of the syndrome of Barraquer-Simons. It must also be borne in mind that many patients oppose the suggestion that they should be observed naked, and this lessens the extension of our observations.

We would thus suggest that *the syndrome of Barraquer-Simons is probably nothing more than an extremely accentuated form of distribution of the adipose pannicle which can be considered as common*, and in consequence there are a whole series of graduations of intermediate forms between the accentuated cases and the normal state.

As is well known, and we have stated above, the syndrome consists of: (1) a tendency of the upper part of the body to grow thin, in which detail we are all in agreement; and (2) a tendency of the lower part to put on fat. Opinions differ as to this second point, for whilst some assert that there is an effective increase of fat, others deny the increase which is only apparent by contrast with the thinness of the upper parts. *Our opinion is that this increase of fat hardly ever exists*, as can be verified when the evolution of the patients is followed for some time. However, occasionally lipomatous formations can be observed, especially in the upper part of the thigh, which increase the volume of the lower limbs.

*In our opinion, then, the essential point is the tendency to thinness of the upper parts, and not only the action of becoming*

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\*La hermosura del tordo, con la cara flaca y el cuerpo gordo.

*thin but also the inability of recovering the adipose panicle.* At the same time the lower part remains normal, unaffected by the cause which makes for thinness, but also untouched by any fattening cause, and yet free to accumulate fat under the action of the inner or outer circumstances which usually make for increase of subcutaneous fat. This is verified if the patient is put on excessive diet and absolute rest; the thinness of the upper parts remains stationary, whilst the lower parts put on fat as in a normal individual. This is shown by the cases of Miraillé and Fortineau (14), Zondek (15) and our own. On the other hand, if the patient is given thyroidine, as we have tried, a normal loss of weight is observed, accentuation of the thinness of the upper parts, and certainly a thinning of the lower limbs, although perhaps less marked than in normal subjects, especially when affected by adipose tumours.

The fusion of fat in the upper part of the body may reach the absolute limits described by some authors. This total re-absorption is characteristic and justifies the qualificative "progressive" given by Simons to this disease. But the extreme limit of this disease appears only in a very limited number of cases and not in all the intermediate cases which, as we have stated, are very numerous. When the fat has disappeared totally the disappearance of the "fat ball" of Bickat is typical, as also the disappearance of the other adipose process of the face, which generally resist persistently all other causes of thinness, even those which are very severe, such as exhausting illnesses, protracted hunger, etc. This circumstance gives the face of the patient that "skull-like aspect" of the total marking of the cheek bones and the whole of the skeleton of the face, under the skin. The coincidence of this total absorption of the fat of the face with a generally normal state of health is in itself sufficient for the diagnosis of the disease.

Apart from these details of the lipodystrophic process there do not appear to be other subjective or objective symptoms of the disease. All other manifestations described by other authors and which we have noted in our own cases, seem to us to be dependent on the other pathological states which almost without exception accompany the lipodystrophy, and which are in a certain sense the "activators" which reveal the disease, but in

no way whatever do we consider that they are directly related to the lipodystrophy itself.

The first observations of this disease were attributed by Barraquer and Simons (3), (4), (13), although with the natural reserve, to neuro-vegetative disturbances. Long and Bickel (8) recently insist on the same hypothesis, in support of which, apart from data as to pathogeny which they themselves admit are doubtful, they allege the frequency with which these patients present nervous vegetative symptoms (which we must admit are almost always of rather vague significance).

Another group of authors have tried to explain the syndrome under consideration by disturbances of the glands of internal secretion. However, in the first place a constant endocrine symptomatology has not been found in cases of lipodystrophy, nor glandular lesions which are not exceptional (it should be borne in mind that autopsies have been very rare), nor the slightest experimental data which support this supposition. In the second place, there is a fact which contradicts the exclusively humoral explanation, and this is precisely the localization of the lesion in only one segment of the body, which could only be explained by intervention of the nervous system. The only anatomo-pathological data at present available on this syndrome are those of Zalla (1), who found a tumour of the hypophysis in a corpse, which had not been under observation during life, but the aspect of which guaranteed the accurateness of the diagnosis, and the case of Sarbo (16), who found a lesion of the corpus striatum.

It seems more logical to admit the collaboration of both these factors, the neuro-vegetative and the endocrine, which it is known appear so frequently united in the clinic, especially in the group of diseases which Pende (17) called "sympathetic-endocrine diseases," or which we might call still more accurately "vegetative-endocrine," such as the different localized lipomatosis, symmetrical lipomatosis and tropho-oedema. This united action would explain why the humoral factor should act only on a certain segment of the organism; at any rate there have been several observations in the clinic which show that this can happen especially in lesions of the hypophysis. For example, Pansini (quoted by Pende, 17), describes a case of hemilateral acromegaly, Biedl (18) mentions another case, and we have also

observed the same (19). Neiden (quoted by Beck, 20), refers to an observation of obesity of hypophyseal origin limited to one side only, and Beck adds that this would not be an exceptional observation if both sides of the organism were measured carefully. Bartolotti (21) published the very interesting case of a man whose left side was attacked by obesity as a consequence of atrophy of the left testicle; and Athias (22) quotes a case of Weber in which a bird had male feathers on the right side of the body and female feathers on the left side, and in which, at autopsy, a testicle was found on the right side and an ovary on the left. The cases of hypophyseal lesion might be interpreted as suggested by Long and Bickel (8) on the supposition that they are not due to an endocrine disturbance but to the lesion of the para-hypophyseal metabolic centers. However, without going into a discussion as to the exaggeration of this effacement of the hypophysis decreed by the physiologists, the cases of Bartolotti and Weber are sufficient for us to affirm that humoral disturbance can act on the tissues in a segmental manner, naturally in collaboration with the nervous system, although the mechanism of this collaboration is not yet known to us.

We do not wish to insist on this suggestion, which for the moment is absolutely theoretical. But we do wish to produce certain data which indicate that *the cephalo-thoracic lipodystrophy is frequently combined with hyperthyroid states and more frequently than with any other pathological state.*

Several years ago Babinski (23) published a case of "Basedow's disease with myxedema in the lower limbs" which we now suspect was hyperthyroidism with lipodystrophy. Gertsmann (24) has described a typical case of lipodystrophy combined with hyperthyroidism. The case of Smith (10) was also hyperthyroidism with hypermetabolism (+ 36%). Christiansen (25) and Feer (26) have also observed the coincidence of lipodystrophy with thyroid ailments, although the latter were not of hyperfunctional type. But we wish to base our arguments chiefly on our own experience.

The first case we reported in 1920 (11), was that of a hyperthyroid patient, although the syndrome of Basedow was not pure but accompanied by melanoderma, virilism and ovarian in-

sufficiency. The observations which we have taken at a later date follow.

#### CASE I

Woman of 48 years. There are several family antecedents pointing to hereditary syphilis (father and two brothers died of juvenile hemiplegia), although she, herself, has had no suspicious manifestation and the Wassermann test was negative. She was very nervous from early girlhood; her first menstruation was at 12 years; she married young and has had 8 children, 7 of whom were still-births. She was stout until 40 years old and began to get thin at 42, becoming more nervous. At 47—that is to say, in the previous year—menstruation stopped and the loss of weight became accentuated until



Fig. 2. Patient, Case I, 12 years previously, in normal health.

at the time of observation she weighs only 45 kilograms for a stature of 1.68 meters (Figs. 2, 3 and 4). The symptomatology we have noted can be divided into the following groups:

On the one hand, we find a typical *hyperthyroid syndrome* corresponding to the form which we have described as "menopause hyperthyroidism" (27): great thinness, discreet thyroid, hypertrophy, tachycardia, trembling, slight exophthalmia, great motor restlessness, sleeplessness, strong hypertensive and emotive reaction with the injection of half a milligram of adrenaline, oculo-cardiac reflex distinctly positive (108-120) and a very high basal metabolism (+ 95%).

On the other hand, an aortic insufficiency can be diagnosed in this patient, well verified by auscultation and percussion, tolerated well by the patient and undoubtedly related to the syphilitic antecedents.

The state of precocious senilism is also very evident in the patient, whose wrinkled face, hard arteries, scanty white hair and general tired face seem to belong to a woman of 60. (Figs. 4 and 5.)



Fig. 3. Patient, Case I, 8 years previously, at the beginning of weight loss.



Fig. 4. Patient, Case I, at the present time.

Finally, even when the patient is dressed one notices clearly the contrast between the extreme thinness of the face, arms and upper part of the body and the normal corpulence of the lower part of the body and the legs. When undressed this contrast is even more marked, the body appearing as if divided by a horizontal line at the height of the waist above which the subcutaneous fat has almost completely disappeared, but has remained below the line in sufficient abundance to form the large suprapubic prominence and the adiposity of the



Fig. 5 Patient, Case I. General aspect.

thighs which are noticeable in the illustration. In brief, it is a typical example of cephalo-thoracic lipodystrophy (Fig. 5).

*Diagnosis:* Climacteric hyperthyroidism; precocious senilism; Syndrome of Barraquer-Simons; aortic insufficiency.

#### CASE II

C. V., 38 years old, married. Her mother died suddenly, and had suffered very much from "palpitations." The patient had menstruated at 15, married at 21, and had 7 children without complica-

tions. She gave a negative Wassermann test. Two years previously she had begun to lose weight and to experience various disturbances, having lost as much as 23 Kgs. up to the time of observation. Our examination gave the following results: Presentation of a hyperthyroid syndrome with large retro-external goiter; fixed stare; slight exophthalmia; trembling; tachycardia; palpitations; sensations of heat; great emotivity; slight lymphocytosis; etc.

On the other hand, we find evident symptoms of mitral insufficiency with blowing systolic murmur and typical radiographic shadow.

Finally, even when the patient is dressed it is obvious that, in spite of the intense loss of flesh, this has not been at the expense of the lower part of the body, which has kept its fat, whilst the upper part shows extreme emaciation. The patient herself expressed her surprise at the phenomenon which was so evident on examining her naked.

*Diagnosis: Retrosternal goiter with hyperthyroidism; Syndrome of Barraquer-Simons; mitral insufficiency.*

#### CASE III

A. S., 30 years old, married. Has had two abortions and one child. At an early age had several infectious diseases and appendicitis. Her mother died insane. She gave a negative Wassermann test. Six years previously, when apparently in good health, she began to lose weight, which in the last four years has reached a loss of 11 kilograms.

With the exception of continued attacks of pharyngitis the patient has nothing more than a hyperthyroid syndrome which, whilst clinically is not very intense, is still perfectly distinct; diffusive hypertrophy of the thyroid, fixed and glassy stare, normal but very unstable pulse, and typical trembling of the hands. The circulatory and nervous reactions to adrenaline are negative. However, the diagnosis of hyperthyroidism is completely confirmed by the determination of the basal metabolism which gives +40%. The oculo-cardiac reflex gives 60-68. The reflex of Hering is positive. The urine is normal.

Examination of the patient when dressed shows the contrast between the extreme thinness of the face (skull-face), thorax above the waist and the width of hips and thickness of the legs (Fig. 6). Undressed examination confirms the existence of the lipodystrophic syndrome, typical but not intense. The patient refuses to be photographed undressed.

*Diagnosis: Hyperthyroidism; Syndrome of Barraquer-Simons.*

#### CASE IV

C. B., 27 years old, has always been healthy and her menstruation regular. She was stout and in normal health when she began to take large amounts of iodine two years previously on the advice of a friend, which gave origin to a typical *syndrome of "Jod-Basedow,"* great loss of weight (12 kgs.), nervousness, anxiousness, sensation of heat, trembling and tachycardia. We should state that she comes from a region where thyroid tumours are endemic (Asturias) and that she had always had a rather heavy neck, and her mother also has a voluminous simple goiter, all of which explains her sensitivity to iodine. At present she is much better. (After discontinuing the iodine for several months her basal metabolism is normal.)

She is herself surprised that the loss of flesh is confined exclusively to the upper part of the body. In effect, her face, thorax and arms are skeleton-like, the disappearance of the fat of the face being extraordinarily intense. On the other hand the adipose panicle

is well maintained from the hips down, giving the typical contrast of the progressive *lipodystrophy*.

*Diagnosis:* Iodine hyperthyroidism and Syndrome of Barraquer-Simons.



Fig. 6. Patient, Case III Cephalo-thoracic type of loss of flesh

#### CASE V

C. N. de G., 57 years old, is married and has no children. She has always been healthy. Her menopause occurred at 48 and about that time a tumour began on the right side with typical hyperthyroid symptoms: thinness, trembling, tachycardia, emotivity, etc., with basal metabolism +20. (At present she is much better.) She showed arrhythmia, dyspnoea of effort and slight cyanosis; initial myocarditis; arterial tension, 180-90.

The patient herself calls attention to the fact that her loss of weight (total 15 kgs.) has been almost all at the expense of the upper part of the body. The fat of the face is completely effaced, giving it

that skull appearance which is characteristic of the lipodystrophy. The lower part of the body maintains its fat perfectly. There is slight œdema in the ankles.

*Diagnosis:* Goiter and climacteric hyperthyroidism; Syndrome of Barraquer-Simons; myocarditis.

#### CASE VII

C. R., 18 years old. Her mother had a large goiter. She herself has suffered during the past two years from a discreet hypertrophy of the thyroid accompanied by tachycardia (110 pulsations), palpitations, trembling and great nervous excitement. During the past year she has begun to lose flesh "from the face and arms only," as she herself remarks.

In effect, the examination of the patient confirms the almost absolute disappearance of the fat from the face, thorax and arms, the inferior part of the body being almost normal (or rather slightly excessive).

She showed basal metabolism, 30; slight lymphocytosis; normal urine.

*Diagnosis:* Juvenile hyperthyroidism; Syndrome of Barraquer-Simons.

Besides these cases, we have seen two more, one published by Pardo (12), and another the history of which we do not copy here, as it reproduces that of any of the known observations in which there were no hyperthyroid symptoms. In consequence, the proportion in favor of the coincidence of lipodystrophy and hyperthyroidism is obvious: 8 cases against 2 of the 10 we have observed.

Loewy and Zondek (28) had already called attention to the frequency with which certain hyperthyroid patients present adiposity in the lower part of the body, but they insist in differentiating these cases from progressive lipodystrophy, arguing that it is simply the appearance of lipomas on the lower limbs, especially at the hips, which give the body the aspect of a false syndrome of Barraquer-Simons. We consider that this interpretation is not correct and that their cases are perfectly similar to ours of lipodystrophy with hyperthyroidism. Examination of the photographs of the cases of Loewy and Zondek convinces us that we are right, although their cases are probably not advanced and the absorption of the fat of the upper parts has not yet reached its maximum intensity. However, there is evidently in these cases a dissociation between the resistance of the lower part of the body and the upper part with respect to the reducing action of the hyperthyroidism. *The fact that the fat takes the form of lipomas and not of diffusive subcutaneous infiltration does not appear to us to be a differential criterion, because the*

*lipomatous formations, either large or small, are present in all forms of obesity, and in many cases it is impossible to determine where the infiltration ends and the lipoma begins.* We do not know exactly the reasons for the formation of lipomas, which are probably of a nervous order and frequently provoked by a peripheral irritation, but as we have stated, this formation takes place in the great majority of stout persons. There is no need to recall the marked frequency with which stout women, especially at the change of life, when they reach a certain degree of adiposity, commence to present lipomas; the classical division of the painful adiposity of Dercum is in simple adipose forms, lipomatotic forms and mixed forms, and finally in our clearest cases of lipodystrophy we have already indicated the presence of more or less developed lipomas. Observation I, as can be seen from the photographs, is a typical example of how the maximum grades of lipodystrophy and hyperthyroidism can be combined.

*Whilst calling attention to this frequency of the combination of hyperthyroidism and lipodystrophy, we repeat that we do not wish to insinuate that the thyroid alteration may be the cause of the trophic disturbance. As we have already indicated, it is probably a neuro-vegetative constitution which predisposes the subjects to this cephalo-thoracic type of thinness, and the hyperthyroidism merely acts as an "activator," exaggerating the tendency of the upper part of the body to lose flesh and the relative resistance of the lower part to this loss, and this resistance is, of course, more apparent when the fat takes the lipomatotic form.*

It could be objected that if this hypothesis were true, any other cause of emaciation would have this same "activating" effect, but it should be borne in mind that hyperthyroidism is precisely a disease which coincides with very constant and profound neuro-vegetative perturbations, which may have part in the lipodystrophic predisposition. In consequence, from this point of view, there is no comparison between a hyperthyroid cachexia and a cancer cachexia, for example. Just as in hyperthyroidism, on the other hand, there would be other cachetic states of endocrine nature, frequently united to neuro-vegetative perturbations also, such as those due to hypophyseal lesions which have also been shown to cause lipodystrophy.

## SUMMARY

Progressive lipodystrophy, cephalo-thoracic lipodystrophy, or syndrome of Barraquer-Simons (syndrome rather than a disease), appears to be a predisposition to a peculiar way of losing flesh, determined by neuro-vegetative factors whose nature we do not yet know.

There are cases, chiefly in women, in which this alteration is what we might call a physiological or attenuated form.

If in such predisposed cases there is an additional cause for losing weight, such cause will act as an "activator" which will accentuate the typical form of loss of flesh. Amongst these causes, the most frequent is hyperthyroidism, undoubtedly because it coincides with favorable neuro-vegetative perturbations which determine the lipodystrophic predisposition.

Whether this hypothesis is correct or not, it is a fact that in practice cephalo-thoracic lipodystrophy frequently coincides with hyperthyroidism, and in every case of lipodystrophy the minor hyperthyroid symptoms should be sought and the basal metabolism be determined. At the same time in every case of flesh. In the lower parts the fat is normal, or at least offers a greater resistance to the loss, especially if lipomatotic formations are produced, as is frequently the case.

From the symptomatological point of view, we consider the essential element of lipodystrophy to be the cephalo-thoracic loss hyperthyroidism the manner of distribution of the fat should be examined. Proceeding in this fashion, we feel sure that our impression will be confirmed as to the frequent co-existence of both states.

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## GIGANTISM\*

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Gigantism is the most interesting and most complex syndrome in pluriglandular affections. It is as interesting as it is little understood, in spite of the careful and lengthy study devoted to this subject by eminent authorities. We find gigantism in all periods of history and among all nations, especially is the Russian epic literature rich with examples of gigantism.

Giants were considered "supermen"; they were clothed with special qualities, with enormous physical strength; the best national characteristics were incorporated in them; every act of theirs became magnified in the songs of the common people.

But our conceptions change with time. At present there is the growing tendency to consider these giants mere pathological types, a form of special affection, that requires a thorough study.

Such patients were not only subjects for extreme curiosity, but also served to be exploited on account of their enormous physical strength. So did Frederick the Great, unmercifully recruit such patients into his army. It was one Piercourt de Saint-Quen, a French baron, that conceived the idea of creating a special fund of several millions of francs to be devoted exclusively to the artificial propagation of giants. This eugenic idea of the baron, however, was a total failure, partly because of the prevalent sterility among giants, and partly because their children as a rule were normal.

The tallest giant on record was Kayanus, a Finn. His height reached 283 cm. It is remarkable that we encounter very few female giants; there are only two females in the following list who have been studied.

1. Fr. Winkelmeyer, Northern Austria, age 20, studied by Virchow, height 278 cm.

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2. Hans Krav, Zimbrass Castle, studied by Kiari, height 275 cm.
3. Konstantin, Württemberg, age 26, studied by Dufreny, height 259 cm.
4. One Scott, skeleton, of Dublin, studied by Freulich, height 259 cm.
5. One Austrian, studied by Topiner, height 255 cm.
6. Marianna Wede, Brenkendorf near Halle, age 16½, studied by Ranke, height 255 cm.
7. Loushkin, a Kalmiuck skeleton, age 33, Orfill's Museum at Paris, studied by Lemolt, height 254 cm.
8. Charles Birn, skeleton, studied by Cunningham, height 253 cm.
9. A Swede, an army guard of Frederick II, skeleton, studied by Topinar, height 252 cm.
10. Cooper, Yorkshire, studied by Ginstel, height 250 cm.
11. "Kaleb," studied by Uds. Gettingson, height 250 cm.
12. Chenoah, Salzburg, studied by Maas, height 250 cm.
13. Wilkins, St. Paul, Minnesota, studied by Virchow, height 245 cm.
14. Hassan Ali, Egyptian, Derr, near Wadi Chalpa, studied by Maas, age 17, height 240 cm.
15. Abul-Choul of Assuan, studied by Sirena, age 20, height 240 cm.
16. Machnoff, Vitebsk, studied by Gushan, age 22, height 238 cm.
17. Drezel, Ohniun, studied by Ranke, age 37, height 238 cm.
18. Schwan-Insing of China, studied by Taruffi, age 33, height 230 cm.
19. Thomas Gessler, Ginund, studied by Boule, age 25, height 235 cm.
20. Amenates, Kerezund, studied by Ornstein, age 18, height 233 cm.
21. Hugo, St. Martin de Versuv, France, studied by Lonoi and Roi, age 25, height 230 cm.
22. Vasilica Callandja, Corinth, age 22, height 230 cm.
23. Yochin Cleicheagvy, Spain, studied by Garnig, height 230 cm.
24. Albert Brug, Scotland, studied by Saltarino, height 230 cm.  
Giants are always descendants of normal sized parents.

Their birth, according to the established view in literature, is not accompanied by any abnormalities. Their growth hardly differs from that of other infants. Their childhood is, as a rule, perfectly normal. Only later, usually before or during adolescence, a tendency of intensive growth develops. This increased growth may be steady or may occur periodically, leaving an interval of comparative rest in growth.

The following case presents so many unusual features that it deserves a full description.

#### PRESENTATION OF CASE

*Patient, V. G., 22, farmer, came into the Therapeutic Clinic of the Second Moscow University at the beginning of February, 1925, with complaints of slight dyspnoea, cough and weakness. He had been sick for the last four years. He is single, has smoked since the age of 17, and occasionally drinks.*

*Heredity.* The grandparents on both sides, paternal as well as maternal, were strong people. His father's mother is still living, her age 80. The patient's father died of tuberculosis of the larynx at the age of 48; he was a drunkard. The mother is living and healthy. She had seven children and two spontaneous miscarriages. She has five living children, of whom one is a daughter of 9 years, of slight build. There was never a case of excessive growth in the family, neither were there any tall ones among all the relatives, according to the statement of the patient's mother.

*Anamnesis.* The patient, the second child, was delivered at full term. He was breast fed and grew extraordinarily rapidly, and his rapid growth, especially at the seventh and eighth months of age, was the talk among the neighbors. In the accompanying photograph (Fig. 1) is seen the patient at the age of eight months sitting on the lap of his mother, while his elder brother of two years is sitting on the father's knee. The man standing is the patient's grandfather on the mother's side. It is clear that the patient at the age of eight months was already physically superior to his two-year-old brother.

This extraordinary growth continued so that at the age of three to four years he was so much taller than his elder brother that no one would believe him to be the younger. At eleven to twelve years his physical strength and growth were the subject of general admiration of the neighbors. At twelve he almost drowned, contracting pneumonia, from which, however, he soon recovered. In spite of this sickness his strength and growth continued to increase. When he was twelve to thirteen years old his father died and he immediately assumed the management of the farm, taking over all the work. This task, according to the patient's own statement, did not seem to him excessively hard. When sixteen to seventeen years old his physical strength was especially in evidence. To carry a bag of flour weigh-

ing five poods (200 pounds) on his shoulder for a distance of four to five versts (miles) was easy for him. His height at this age increased considerably. There was no one to equal him in the whole county, either in strength or in growth.

In 1921, when the patient reached his eighteenth year, he again contracted pneumonia, followed shortly after by an attack of typhoid fever. Soon after recovery from these diseases he accidentally fell off a swing from a height of fourteen feet and was unconscious for two hours, but fully recovered and for a time felt himself the same



Figure 1. Patient at the age of eight months.

as ever. Soon, however, he gradually began to notice an oncoming weakness and the ceasing of growth. At the same time he noticed a slight thoracic kyphosis.

*Present Status.* The patient's height is 193.4 cm., and his weight, 87.5 kg. His powerful build is evident in his whole appearance. His head is not large, its circumference being 56.8 cm. The superciliary arches are definitely thickened and are quite prominent. The bones of the skull as well as all the bones of the face are quite thickened.

The eyes are widely separated. The root of the nose is somewhat depressed. The nostrils are widely open. The lower jaw is directed decidedly forward and is of powerful size. The teeth are considerably spaced, especially in the lower jaw. The tongue and the ears are very small, out of proportion to the other parts of the head. He has a good growth of hair on his head. There is no beard, however, nor a mustache, and he never has had either. On swallowing there appears on the neck a circular swelling coming out from behind the manubrium sterni. This is the right lobe of the thyroid gland, which



Figure 2. Patient W. G-ow is 22 years old, and his mother is 50.

is quite enlarged and situated low. The larynx is large, the thyroid cartilage measures much more than usual. The circumference of the neck is 43 cm.

The thorax is strikingly large, the ribs are thickened, the intercostal spaces widened; the diverging angle of the ribs is considerably more than a straight angle. The respiration is of mixed type. On the back one immediately notices the enormous scapulae and the spinal column, which is in its upper thoracic segments disfigured by kyphosis. Hair under the axillae is moderately present. There is com-

plete absence of hair on the chest. The abdomen is not enlarged and is not fat. The suprapubic growth of hair is of the feminine type. The penis is large, the testicles are each the size of a large plum. Erections and libido are present. The pelvis is of the male type and powerful. The extremities are proportionately large and wide. The hands are very large.

The patient's skin is devoid of any abnormalities, as eruptions or scars. Pirquet's reaction is negative. The roentgenological examination of the skeleton reveals a considerable thickening of all the bones, equally distributed.

The roentgenography of the skull reveals a definite enlargement and thickening of the lower maxilla, of the malar bone, and of the superciliary arches. The sella turcica, due to rhythmical pulsatory movements of the head, could not be obtained clearly. It appears, however, somewhat wider and deeper than normal. The anthropometric measurements of the patient in millimeters are as follows:

	Weissenberg's		Our Patient	
	Patient		Abs.	Rel.
Height, standing .....	1658	1000	1934	1000
Height, sitting .....	873	526	1919	529
Measurement of lower segment....	785	475	924	479
Circumference of thorax.....	836	508	1115	575
Length of arms.....	748	451	860	446
Length of legs.....	863	520	950	492
Width of shoulders .....	361	218	450	233
Width of hips .....	276	166	340	176
Circumference of head .....	551	332	586	304
Length of hand.....	185	112	220	114
Length of foot.....	258	157	300	156
Weight.....	58.51 kg:		87.5 kg.	

*The Respiratory Organs.* The thorax is bulky. Over the right apex there is a slight depression. Percussion here reveals a slight dullness. The lung borders are within normal limits. The lungs are very large (manifestations of splanchnomegaly). Auscultation everywhere reveals vesicular respiration and dry scattered râles. Over the right apex is heard bronchial respiration. The sputum is negative.

*Circulation Organs.* The lines of demarcation of the heart (by percussion) are within normal limits, the left border being one finger width inside of the left nipple line, the right border in the third intercostal space, but of course the whole dullness of the heart is proportionately large. The large vessels by roentgenography do not show any abnormality. On auscultation dull sounds and light systolic murmurs are heard at the apex and especially over the "pulmonary area." The pulse is 80, regular, full and tense.

*Digestive Organs.* He has excellent appetite and no dyspeptic symptoms. The stomach juices proved upon examination to be en-

tirely normal. The examination of the duodenal contents, obtained through the introduction of a thin catheter, gave the following results:

Trypsin, 2560  
Diastase, 640  
Lipase, 7.4

A few leucocytes were found in the sediment. The examination of the feces showed the presence of ascaris eggs. The liver and the spleen are not palpable. The abdomen is negative.

*Genito-Urinary Organs.* The urine is normal. Urination does not show any deviation from normal. The penis, as mentioned before, is proportionately large; testicles, the size of large plums. The patient states that he has libido and quite frequent erections. He has frequently thought of marriage, but poverty has stood in the way. He denies onanism.



Figure 3. On the left is the patient's hand, on the right is the hand of a normal healthy man of the same age as the patient.

#### *Blood Examination.*

Wassermann's negative.

Hemoglobin,	80%
Erythrocytes,	4,600,000
Leucocytes,	7,300
Neutrophiles,	61.5%
Small lymphocytes,	22.5%
Large lymphocytes,	6. %
Eosinophiles,	8. %
Transitional cells,	1.5%
Basophiles,	0.5%

The large percentage of eosinophiles, which is quite common in acromegaly, may be noted. But this symptom becomes of no value in our case, because of the presence in the feces of ascarid eggs. There is nothing unusual in his nervous system, except the lower knee reflex. Psychologically the patient presents many abnormalities. The consciousness and the orientation as to space, time and surroundings are clear. The patient is and has been mentally backward since childhood. The disease did not add any other changes in his psychical condition. His self-consciousness and his mood are firm; he is even, quiet, not irritable and not excitable. He lacks a clear idea of his present condition, considering himself practically well. His asthma troubles him only on walking; he has no other complaints. He believes that if he were at home he would be quite well. The circle of his interests is very narrow; he leads a hand-to-mouth existence. He desires to learn carpentry, but in case he does not succeed, he would be as well satisfied with his present peasantry. He loves quietude, order and rest. He always avoids disputes, quarrels and fights, in spite of his superior physical strength. Being always able to prove his right by his might, he nevertheless never takes advantage of it. He enjoys the love of his neighbors for his even temper and helpfulness.

He graduated from a primary peasant school; he was far from good in his studies, which he pursued against his wish and without any order. He never had any love for books. He is not able to name a single Russian writer, neither can he name any country or government, except the Soviet Republic and its President, Kalinin. He counts correctly with relative ease and dexterity. Within the limits of his possibilities his thinking is quite logical. He has no delirious or fixed ideas, neither has he any hallucinations. His personality is intact. He is drowsy, apathetic, somewhat draggled.

*Sensory Organs.* The sight and eye backgrounds are normal. There is no bitemporal hemianopsia. Hearing and smell are normal.

Considering all the facts obtained from the patient we see that they amount to a chronic myocarditis, bronchitis and the consolidation of the right apex in a subject of twenty-two years, of gigantic stature, with prominent acromegalic stigmata—enlarged superciliary arches, molar bones, nose, lower jaw, larynx, wrists and ankles. There is present also a small right sided goitre.

The whole history of his growth is uncommon. In the literature, as a rule, we find the appearance of gigantism corresponding with the advent of sexual maturity; here the infant of eight months outgrew his brother of two years. His growth progressed slowly and without regard to his sexual development. With this growth his physical strength increased proportionately.

The study of gigantism began with the appearance of the work of Langer (1872), who differentiated two kinds of giants, the "normal" and the "pathological" (acromegalic). The ex-

istence of so-called "normal" giants is questionable. Though Langer described three skeletons of "normal," "harmonious" giants, yet we know that in all giants sooner or later there appear acromegalic symptoms. Sternberg had shown that in 40 per cent of giants is present acromegaly, and that 20 per cent of acromegalic patients are giants. Thus gigantism and acromegaly are so closely interwoven that it is impossible to determine the end of one and the beginning of the other. Launnois and Roy state that the majority of the giants they observed had acromegaly. The period of their stormy growth coincided with their sexual maturity. Their sexual vigor died out early; as a rule they were childless. They became weak at an early age and died of accidental causes, resembling the early withering of an artificially raised flower. The giant observed by Huchard and Launnois began his stormy growth at the age of 12. At 18 his height was 197 cm. He had two children. He reached the age of 60, when the symptoms of acromegaly appeared.

Brissaud and Meige expressed the view that acromegaly and gigantism are symptoms of the same affection, a disorder of the hypophysis. In young individuals this affection brings forth gigantism, while in older individuals where the ossification of the epiphyseal sutures is complete the same affection will result in acromegaly.

The assertion of these authors that gigantism is an acromegaly of growth is positively wrong, because we know from literature of many cases of acromegaly in children, and in 1912 Salle described a case of an innate acromegaly of a newborn. Post-mortem examination revealed a dilated sella turcica; the hypophysis contained a number of shoots of eosinophilic elements that were diffused in the whole anterior portion. Berroletti in 1910 described a young man of 19 who, at 14, developed typical acromegaly. His height was 166 cm. All the epiphyseal junctures were open. There was no gigantism. Fisher reported a case of acromegaly in an 11 year old boy. His height was normal. Claude described a 19 year old girl, where acromegaly appeared at the age of 15. Here again there was no gigantism. The epiphyseal junctures were closed. Thus we see that acromegaly may appear at an early age and that

its development does not depend upon the condition of the epiphyseal junctures.

The close relationship, however, between gigantism and acromegaly may be considered definitely established. The more carefully the giants have been studied, the oftener have been found in them the changes of the sella turcica and the oftener they have been classified as acromegalic.

Levy and Franchini pointed out the fact that giants frequently develop hypophyseal obesity, which is often met also in acromegalics.

Assuming that in both cases the posterior portion of the hypophysis becomes compressed by the changed anterior glandular portion, we can see in it another proof of the pathogenic relationship of these diseases. There is an undoubted presence of some common pathogenesis, but it is hard to determine the nature of it. It is merely clear that in both cases there are certain hyperplastic changes in the anterior portion of the hypophysis. Why in one case develops gigantism, in the other acromegaly, we do not know. It is possible that in gigantism there is a pure hyperplasia of the cellular elements which causes a hypersecretion of the anterior portion of the hypophysis, resulting in the hypersecretion of the normal hormone that leads to gigantism. This is confirmed by a series of experiments in which, after feeding animals on an abundant diet, consisting of hypophysis preparations (the whole pituitary, or the anterior portion of it, but not the posterior), the manifestations of gigantism appeared.

As to acromegaly, which is as a rule caused by an adenoma of the anterior portion of the hypophysis, developing from the eosinophilic elements, we have to suppose that the blood stream receives an abundance of a chemically abnormal secretion. This may have been the cause of changes in the patient's organism that led to acromegaly. Of course, this is a mere hypothesis.

It may be in place now to mention the classification of gigantism by Launnois and Roy. They divide this disorder according to its pathology into two kinds:

- (1) Acromegalic gigantism, the result of hyperfunction of the anterior portion of the hypophysis;
- (2) Eunuchoid gigantism or infantile gigantism in which

primary hypogonadism leads to the secondary hyperpituitarism.

Falta finds it quite difficult to give a clear, characteristic description of gigantism. This carefulness is fully justified, because after all, we know only that gigantism and acromegaly are related to each other but are far from being identical. As is generally accepted now, acromegaly results from adenoma of the eosinophilic elements in the anterior portion of the hypophysis, while there are other changes in the hypophysis that are limited to hyperplasia of the cellular elements that may lead to gigantism.

This would also explain the frequency of anomalies in the eyes in acromegaly: the failure of the eyesight, due to pressure exerted upon the optic nerve; the limited visual field (temporal hemianopsia) while these eye symptoms are only rarely observed in gigantism. In our case there is also the absence of any eye symptoms. It is possible, however, that in time the present clinical picture may radically change towards a larger degree of acromegaly.

As to therapeutic measures in gigantism, we consider it a disease that requires treatment, especially when, as in our case, the acromegalic stigmata appear. There was hardly any need of symptomatic treatment in our case, as there was an entire absence of the usual complaints in acromegaly—of headaches, rheumatic pains, etc. Again there was no indication for organotherapy, which in this case would be the preparations from the sexual glands. There was also no necessity for any operative interference, there being no reason to believe in the presence of a tumor in the hypophysis. Thus the only thing left to us was roentgenotherapy. As the patient presented undoubtedly symptoms of acromegaly, it is most likely that the supposed hyperplasia of the anterior portion of the hypophysis had already begun to acquire an adenomatous character. Hence the atrophic influence of the roentgen rays seemed to us the proper therapeutic agent. The treatment was given under direct supervision of Dr. Eisenstein. The patient received a full erythema dose.

Gramegna in 1909 was the first successfully to employ roentgenotherapy. Then in 1913 Béclère and other roentgenologists followed. Steiger collected 20 cases up to 1920, in

which roentgenotherapy was employed. In 1922, Kortschalowsky and Eisenstein also used this method with good results in treating acromegaly. The eye symptoms improved rapidly. This prompted us to apply the same method of treatment in our case as an *ultimum refugium* in the hope that we may at least check the acromegalization of our giant.

The results the future will show.

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STUDIES OF THE THYROID APPARATUS. XXX. THE  
RELATION BETWEEN AGE AT INITIATION OF  
AND RESPONSE OF BODY GROWTH TO  
THYROID AND PARATHYROID  
DEFICIENCY

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INTRODUCTION

The time has now come when it is possible to gather together and interpret in orderly fashion the accumulated data of nearly six years of experimentation designed to make possible an evaluation of the part played by the thyroid and parathyroid glands in the growth of the mammal. A continuous supply of material (*Mus norvegicus albinus*) of uniform history kept under uniform conditions of diet and environment (1) has made possible a comprehensive study of this problem, in which is included a determination of the relative importance at different stages of development of the functions mediated by these glands in growth; a determination of the sex differences in growth response to their deficiency; and a determination of the differential growth sensitivity of the various organs to thyroid and parathyroid lack.

Previous papers of this series, in which the results of thyro-parathyroidectomy and parathyroidectomy at 75 and 100 days of age have been discussed, give the scope of the investigation, the mode of procedure, the methods of analysis, and the criteria used in determining the success of the operative technique. The numerical distribution of the animals according to age at time of operation, type of operation, sex and controls is to be found in the twenty-ninth paper of the series (2). This paper deals with the relative growth of the body in weight and length and the tail in length of the male and female albino rats subsequent to the glandular removals at the different ages (23, 30, 50, 65, 75 and 100 days).

In table 1 are given the initial and terminal mean values

TABLE 1

Observed Mean Values of Body Weight, Body Length and Tail Length

Age	Thyroparathyroidectomized						Parathyroidectomized			
	At Beginning			At End			At Beginning		At End	
	Ref.	Conts.	Controls	Tests	Controls	Tests	Controls	Tests	Controls	Tests
MALES—BODY WEIGHT										
23	27.5 <sup>a</sup>	30.2 <sup>b</sup>	30.5 <sup>c</sup>	30.5 <sup>d</sup>	271.3 <sup>e</sup>	192.6 <sup>f</sup>	28.5 <sup>g</sup>	27.5 <sup>h</sup>	275.5 <sup>i</sup>	181.7 <sup>j</sup>
30	41.4 <sup>a</sup>	40.0 <sup>b</sup>	39.8 <sup>c</sup>	39.7 <sup>d</sup>	264.3 <sup>e</sup>	170.4 <sup>f</sup>	41.7 <sup>g</sup>	43.3 <sup>h</sup>	281.9 <sup>i</sup>	202.9 <sup>j</sup>
50	74.5 <sup>a</sup>	77.6 <sup>b</sup>	80.7 <sup>c</sup>	80.7 <sup>d</sup>	255.2 <sup>e</sup>	174.6 <sup>f</sup>	78.5 <sup>g</sup>	78.1 <sup>h</sup>	258.7 <sup>i</sup>	184.3 <sup>j</sup>
65	120.8 <sup>a</sup>	112.2 <sup>b</sup>	119.8 <sup>c</sup>	119.8 <sup>d</sup>	246.0 <sup>e</sup>	175.6 <sup>f</sup>	122.6 <sup>g</sup>	122.7 <sup>h</sup>	257.0 <sup>i</sup>	169.3 <sup>j</sup>
75	133.2 <sup>a</sup>	133.8 <sup>b</sup>	137.2 <sup>c</sup>	137.2 <sup>d</sup>	229.8 <sup>e</sup>	183.9 <sup>f</sup>	139.9 <sup>g</sup>	132.0 <sup>h</sup>	229.8 <sup>i</sup>	147.2 <sup>j</sup>
100	162.3 <sup>a</sup>	163.8 <sup>b</sup>	160.0 <sup>c</sup>	160.0 <sup>d</sup>	229.8 <sup>e</sup>	180.0 <sup>f</sup>	163.8 <sup>g</sup>	156.7 <sup>h</sup>	229.8 <sup>i</sup>	192.8 <sup>j</sup>
MALES—BODY LENGTH										
23	95.3 <sup>a</sup>	100.8 <sup>b</sup>	113.6 <sup>c</sup>	113.6 <sup>d</sup>	211.0 <sup>e</sup>	185.6 <sup>f</sup>	97.8 <sup>g</sup>	95.0 <sup>h</sup>	213.6 <sup>i</sup>	185.6 <sup>j</sup>
30	116.1 <sup>a</sup>	120.4 <sup>b</sup>	130.9 <sup>c</sup>	130.9 <sup>d</sup>	214.3 <sup>e</sup>	179.4 <sup>f</sup>	115.3 <sup>g</sup>	114.9 <sup>h</sup>	214.4 <sup>i</sup>	191.4 <sup>j</sup>
50	149.2 <sup>a</sup>	161.1 <sup>b</sup>	163.4 <sup>c</sup>	163.4 <sup>d</sup>	207.4 <sup>e</sup>	180.4 <sup>f</sup>	140.2 <sup>g</sup>	137.4 <sup>h</sup>	200.4 <sup>i</sup>	186.4 <sup>j</sup>
65	169.3 <sup>a</sup>	161.1 <sup>b</sup>	167.5 <sup>c</sup>	167.5 <sup>d</sup>	211.2 <sup>e</sup>	185.3 <sup>f</sup>	163.9 <sup>g</sup>	164.6 <sup>h</sup>	214.3 <sup>i</sup>	180.9 <sup>j</sup>
75	174.8 <sup>a</sup>	167.5 <sup>b</sup>	169.8 <sup>c</sup>	169.8 <sup>d</sup>	206.4 <sup>e</sup>	186.7 <sup>f</sup>	171.1 <sup>g</sup>	167.7 <sup>h</sup>	208.4 <sup>i</sup>	182.2 <sup>j</sup>
100	182.5 <sup>a</sup>	180.0 <sup>b</sup>	202.5 <sup>c</sup>	202.5 <sup>d</sup>	178.7 <sup>e</sup>	186.5 <sup>f</sup>	180.0 <sup>g</sup>	175.8 <sup>h</sup>	202.5 <sup>i</sup>	180.9 <sup>j</sup>
MALES—TAIL LENGTH										
23	67.5 <sup>a</sup>	70.7 <sup>b</sup>	70.2 <sup>c</sup>	70.2 <sup>d</sup>	180.8 <sup>e</sup>	153.4 <sup>f</sup>	70.4 <sup>g</sup>	68.3 <sup>h</sup>	187.4 <sup>i</sup>	161.3 <sup>j</sup>
30	85.7 <sup>a</sup>	87.0 <sup>b</sup>	84.0 <sup>c</sup>	84.0 <sup>d</sup>	187.9 <sup>e</sup>	149.4 <sup>f</sup>	87.1 <sup>g</sup>	80.7 <sup>h</sup>	189.6 <sup>i</sup>	165.9 <sup>j</sup>
50	110.3 <sup>a</sup>	121.0 <sup>b</sup>	122.5 <sup>c</sup>	122.5 <sup>d</sup>	182.1 <sup>e</sup>	154.3 <sup>f</sup>	119.2 <sup>g</sup>	122.3 <sup>h</sup>	181.3 <sup>i</sup>	165.1 <sup>j</sup>
65	145.1 <sup>a</sup>	134.9 <sup>b</sup>	141.5 <sup>c</sup>	141.5 <sup>d</sup>	175.9 <sup>e</sup>	144.0 <sup>f</sup>	144.0 <sup>g</sup>	143.8 <sup>h</sup>	182.1 <sup>i</sup>	164.3 <sup>j</sup>
75	146.4 <sup>a</sup>	144.6 <sup>b</sup>	148.3 <sup>c</sup>	148.3 <sup>d</sup>	173.9 <sup>e</sup>	159.9 <sup>f</sup>	156.6 <sup>g</sup>	145.2 <sup>h</sup>	172.1 <sup>i</sup>	160.1 <sup>j</sup>
100	155.9 <sup>a</sup>	158.6 <sup>b</sup>	154.3 <sup>c</sup>	154.3 <sup>d</sup>	172.2 <sup>e</sup>	159.3 <sup>f</sup>	158.6 <sup>g</sup>	155.3 <sup>h</sup>	172.2 <sup>i</sup>	163.9 <sup>j</sup>

TABLE 1—Continued

Observed Mean Values of Body Weight, Body Length and Tail Length

Age	Thyroparathyroidectomized						Parathyroidectomized					
	At Beginning			At End			At Beginning			At End		
	Ref.	Conts.	Controls	Tests	Controls	Tests	Controls	Tests	Controls	Tests	Controls	Tests
FEMALES—BODY WEIGHT												
23	25.5±0.7	27.3±0.9	26.5±0.8	102.5±1.6	135.8±6.0	31.5±1.2	30.5±1.0	105.5±3.1	142.0±5.3	14.5±0.3	14.5±0.3	
30	38.2±0.8	37.2±1.1	36.7±1.1	103.3±3.5	122.8±1.1	10.2±1.4	10.1±1.1	180.8±3.0	159.0±4.2	15.0±1.2	15.0±1.2	
50	70.2±0.8	75.7±3.7	71.2±3.0	172.1±3.6	115.0±5.0	70.8±2.7	76.7±2.1	176.7±2.5	135.6±1.9	135.6±1.9	135.6±1.9	
65	106.0±1.6	106.8±3.2	106.3±3.0	181.1±2.0	133.0±6.8	107.5±2.1	101.5±2.1	182.2±8	139.0±2.7	132.0±5.7	132.0±5.7	
75	115.8±2.6	117.3±2.6	117.5±3.1	178.5±3.4	123.0±3.1	100.5±3.1	111.1±2.8	108.6±5.6	132.0±5.4	111.1±4.1	111.1±4.1	
100	137.6±2.2	111.5±3.9	110.8±3.7	177.0±1.3	130.8±1.2	111.5±3.0	137.0±1.0	177.0±1.3	111.1±1.1	111.1±1.1	111.1±1.1	
FEMALES—BODY LENGTH												
23	98.0±0.8	95.7±1.0	93.8±0.9	103.4±0.6	105.5±2.8	99.0±1.0	97.9±0.8	101.0±1.2	101.3±2.0	171.3±2.0	171.3±2.0	
30	108.8±0.6	108.9±1.1	107.8±1.5	101.3±1.2	102.0±1.5	102.0±1.7	108.0±1.3	103.0±1.2	103.0±1.3	170.2±1.0	170.2±1.0	
50	114.8±1.0	139.1±2.1	136.0±2.0	107.7±1.1	111.5±1.5	111.5±1.7	139.3±1.3	139.3±1.3	139.3±1.3	170.5±1.3	170.5±1.3	
65	161.8±0.9	157.1±1.2	152.8±1.0	100.0±1.0	171.5±1.0	139.1±1.1	135.0±1.2	192.1±1.0	192.1±1.0	176.1±2.1	176.1±2.1	
75	166.8±1.3	161.6±1.9	159.1±2.5	180.1±0.9	170.0±1.0	159.5±1.1	159.5±1.5	195.1±1.6	172.3±2.0	172.3±2.0	172.3±2.0	
100	177.1±0.9	171.5±1.5	171.5±1.7	190.2±1.3	176.0±1.4	171.5±1.5	165.0±2.0	190.2±1.3	177.3±1.8	177.3±1.8	177.3±1.8	
FEMALES—TAIL LENGTH												
23	71.3±0.6	69.3±0.7	66.5±1.1	170.2±0.9	138.2±3.7	73.5±0.7	71.7±0.7	170.1±1.7	170.1±1.7	151.3±1.6	151.3±1.6	
30	86.3±1.0	84.9±1.1	83.1±1.1	166.7±2.6	138.8±2.0	89.0±1.5	88.0±1.5	169.8±2.7	169.8±2.7	161.8±1.6	161.8±1.6	
50	120.1±1.7	122.7±3.3	119.7±2.1	167.7±2.1	110.8±1.3	120.3±2.3	123.5±1.5	170.0±1.3	170.0±1.3	151.3±1.6	151.3±1.6	
65	141.0±1.7	139.8±1.5	137.0±2.2	165.0±1.7	111.7±1.6	111.7±1.6	139.0±1.7	167.6±1.0	167.6±1.0	157.5±1.8	157.5±1.8	
75	143.9±1.1	146.7±2.3	137.1±2.3	163.2±1.4	152.1±2.0	145.0±1.6	148.6±1.4	162.1±0.7	162.1±0.7	159.7±1.5	159.7±1.5	
100	152.6±1.3	153.3±1.2	151.6±1.1	165.5±1.3	156.6±1.1	153.3±1.2	152.3±1.9	163.5±1.3	163.5±1.3	157.3±1.8	157.3±1.8	

The "Beginning" values are those observed at the ages given in the first column : the "End" values those observed at 150 days of age, the end of the period of observation for all groups.

TABLE 2  
The Absolute and Relative Percentage Growth in Body Weight, Body Length and Tail Length.

Age Series	Thypars			Parathys		
	Conts	Tests	T/C	Conts	Tests	T/C
MALES BODY WEIGHT						
23	798 34	539 87	67 6	878 63	568 01	64 6
30	560 75	328 14	58 5	576 02	368 59	64 0
50	228 87	116 36	50 8	229 55	135 98	59 2
65	137 97	46 58	33 8	131 83	37 98	28 8
75-	83 86	33 45	39 9	83 70	11 52	13 8
100	40 29	12 50	31 0	40 29	23 04	57 2
MALES BODY LENGTH						
23	109 32	89 39	81 8	118 40	95 37	80 5
30	88 64	60 14	67 8	89 42	66 58	74 5
50	48 78	30 44	62 4	49 36	35 66	72 2
65	31 10	13 54	43 5	30 75	13 55	44 1
75	23 22	9 95	42 9	21 80	8 65	39 7
100	12 50	4 36	34 9	12 50	8 02	64 2
MALES TAIL LENGTH						
23	155 73	118 52	76 1	166 19	136 16	81 9
30	115 98	77 86	67 1	117 68	91 35	77 6
50	50 50	25 96	51 4	52 52	35 00	66 6
65	30 39	10 95	36 0	26 46	14 26	53 9
75	20 26	7 82	38 6	17 48	8 08	46 2
100	8 58	3 24	37 8	8 58	5 54	64 6
FEMALES BODY WEIGHT						
23	606 23	417 56	68 9	521 02	370 20	71 1
30	420 70	237 36	56 4	372 13	305 08	82 0
50	127 34	56 20	44 1	121 43	76 79	63 2
65	69 89	37 59	53 8	69 55	37 54	54 0
75	52 17	9 24	17 7	53 88	16 17	30 0
100	25 09	—7 11	—28 3	25 09	5 18	20 6
FEMALES BODY LENGTH						
23	102 09	76 44	74 9	96 57	75 15	77 8
30	78 42	50 83	64 8	74 66	64 55	86 5
50	39 08	18 75	48 0	34 13	23 12	67 7
65	21 09	12 24	58 0	21 51	13 61	63 3
75	17 20	7 21	41 9	17 03	8 50	49 9
100	10 90	2 62	24 0	10 90	5 09	46 7
FEMALES TAIL LENGTH						
23	145 60	107 82	74 1	131 43	115 20	87 7
30	96 35	66 43	68 9	90 15	82 00	91 0
50	36 67	17 63	48 1	34 60	24 94	72 1
65	18 03	6 13	34 0	18 28	12 82	70 1
75	11 25	3 39	30 1	11 79	7 47	63 4
100	6 65	1 36	20 5	6 65	3 28	49 3

for the various groups of the several age series, together with their probable errors. In table 2 are given the absolute percentage increments and the relative increments of the tests in terms of those of their controls, the values being derived from the data in table 1. In order to facilitate analysis by visualization the relative values have been charted. Chart 1 shows the sex differences, chart 2 the differences in body weight, body length and tail length, and chart 3 the differences in response to the two types of glandular deficiency.

#### AGE DIFFERENCES

It is clear from both tables and charts that growth in body weight, body length and tail length of both sexes is retarded by the production of a thyroid or parathyroid deficiency at each of the stated ages. I shall consider the retardation following thyro-parathyroidectomy as an expression of a reaction to *thyroid* deficiency for the reasons which have been given in the preceding paper (2). The retardation following parathyroidectomy is obviously attributable to a parathyroid deficiency (3).

From charts 1 and 2 it is at once evident that the degree of growth retardation in body weight, body length and tail length in both sexes subsequent to the initiation of a thyroid deficiency increases with the age of the animal at the time of glandular removal. The older the animal the more it is dependent upon thyroid function for normal growth. This was indicated in an earlier study and is now confirmed and established (4). The detailed explanation of the phenomenon with respect to growth in body weight has been given in the preceding paper (2) and need not be repeated. The principle is extensible to growth in body and tail length. It is based on the well known fact, which needs no demonstration, that the normal rate of growth decreases with advancing age, and the fact that growth by increase in cell mass becomes with increasing age progressively a greater proportion of total growth while growth by increase in cell number becomes progressively a smaller proportion. In this shift in ratio the importance of the thyroid in growth increases with the increase in proportion of growth by increase in cell mass, because the role of this gland in growth is that of a participant in the regulation of

the metabolic level, through which is determined the rate of the maintenance processes of the organism and hence the amount of material presented to the cells for growth purposes during a given period. Hence the older the animal the more it is dependent on thyroid function for normal growth.

Now although the generalization given above that the direction of change in degree of retardation increases with increasing age at the time of thyroid removal is valid, an inspection of charts 1 and 2 shows that the course of the progression is divisible into two periods; the period before and the period after the incidence of puberty (from 23 to 65 and from 65 to 100 days of age). Up to and including the 65-day-old series

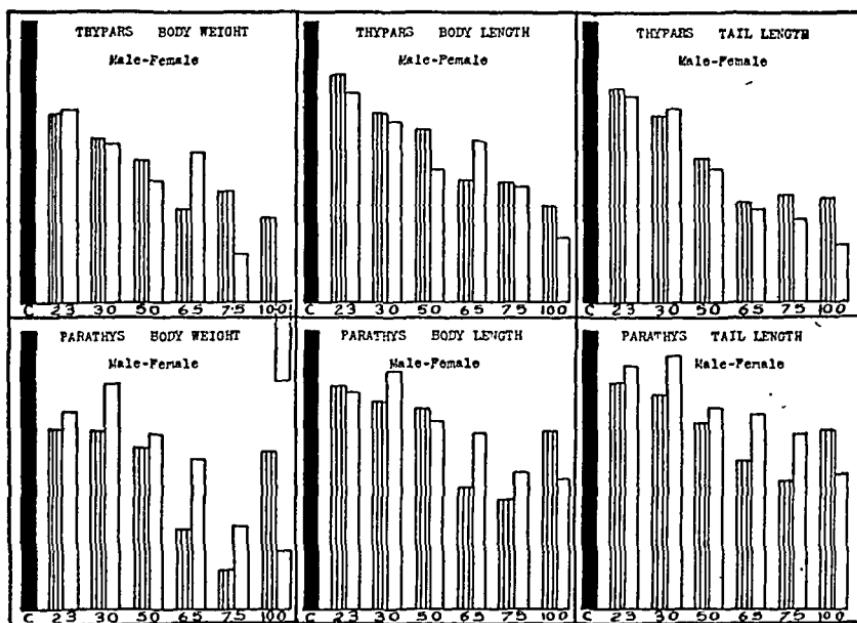


Chart 1. The growth in body weight, body length and tail length of the test groups in terms of that of their controls arranged for sex comparison.

the increase, in the males, is consistent and marked; while from 65 days on the degree of change is quantitatively negligible, though of course directionally significant. Puberty has evidently introduced a new factor conditioning the degree of response to thyroid deficiency in both sexes and which in the males tends towards stabilization. This tendency at this stage of development has been noted in bone growth and differentiation (5) (6) (7) (8) and in the course of growth in body weight

of these thyroidless rats of the 23, 30, and 50-day-old series (2). In the females, puberty conditions a different type of response, viz., an increase in resistance to thyroid deficiency initiated at 65 days of age as compared with the reaction of the 50-day-old group; while the retardation in the 75 and 100-day-old groups is markedly and progressively greater instead of tending towards stabilization. While these sex differences in details exist, they do not cloud the principle of a pubertal modification of growth response to thyroid deficiency.

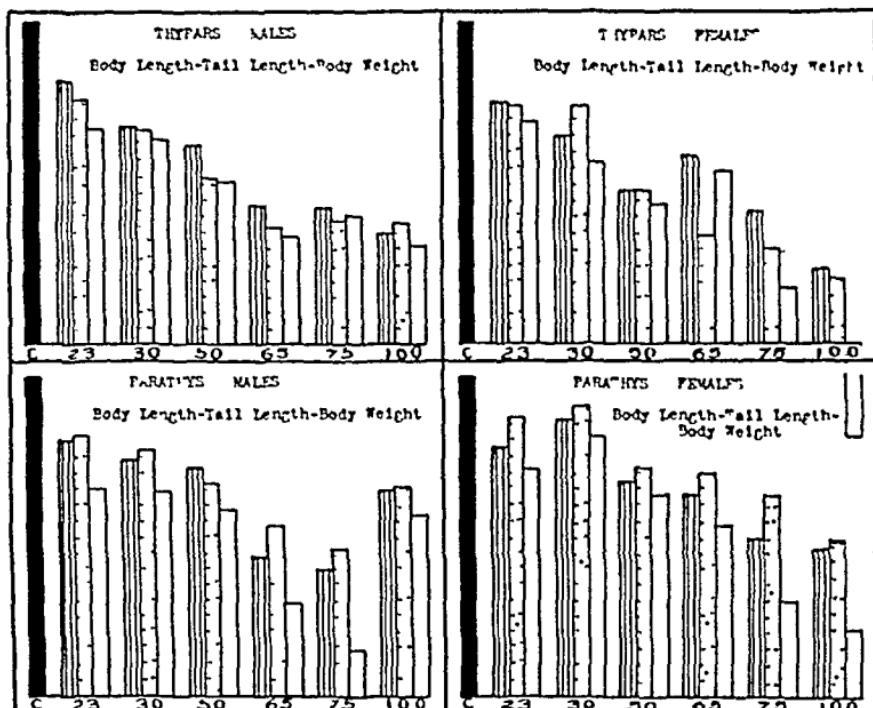


Chart 2. The growth of the various test groups in terms of that of their controls arranged for comparison of body weight, body length and tail length

Turning now to the parathyroidless groups it is seen from charts 1 and 2 that increasing age at time of glandular removal conditions in general an increasing subsequent growth retardation in body weight, body length and tail length. This progression indicates a fundamental similarity in organic reaction to both types of glandular deficiency. The relation has been analyzed and discussed in the previous paper (2). It is based on the idea that growth retardation following parathyroid removal is largely attributable to a lowering of the nutrient level

because of a disturbance in the effectiveness of the digestive system. Combined with this there is, of course, the increased maintenance utilization of metabolites caused by the mild but chronic tetany.

The increase in gross growth retardation with increasing age at time of initiation of the parathyroid deficiency is explicable on the basis of the interaction of these two phenomena. For as the growing animal becomes older it uses a progressively lesser proportion of metabolites for growth and a progressively larger proportion for maintenance. Hence a restriction of the available nutrients combined with a relative increase in the de-

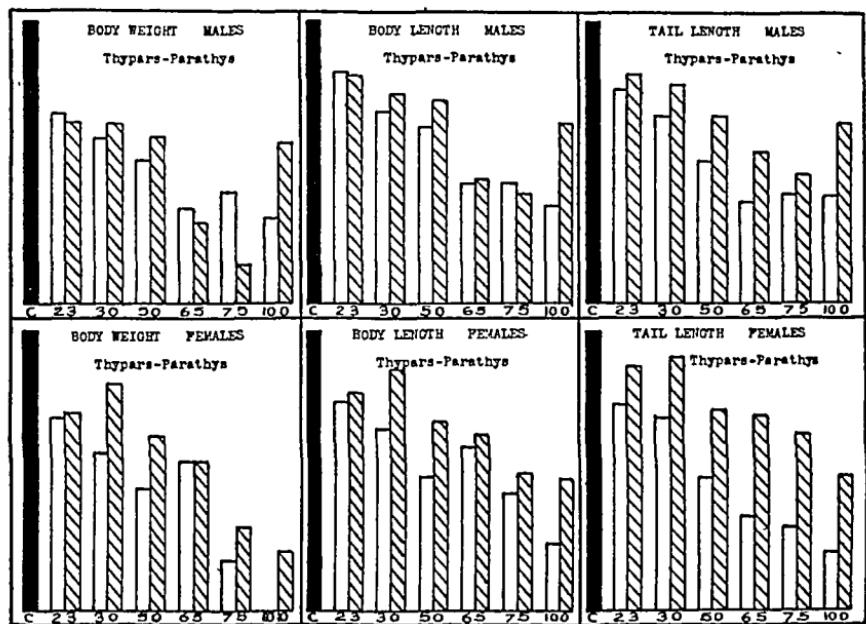


Chart 3. The growth in body weight, body length and tail length of the tests in terms of that of their controls arranged for comparison of the response to thyroid and parathyroid deficiency.

mand on the part of the maintenance processes would of necessity cause a progressively greater than normal reduction in the proportion of materials used for growth purposes with increasing age of the animal at the time of the initiation of the metabolic disturbance; an expression of which would be a progressive increase in general growth retardation.

This interpretation fits the observations. Others that suggest themselves are incomplete or not in accord with the facts. For instance it might be said that the phenomenon is an ex-

pression of an increasing sensitivity to the toxemia as such. This explanation fails to take into account the fact that older animals are less susceptible than younger to death from tetania parathyreopriva. It might be said that since the metabolic rate of young animals is greater than that of older, the disposal of toxic products is more easily effected and hence growth is less retarded. But if we assume, as I believe it just to do, that the toxic products are endogenously produced, it is obvious that these would be formed in larger relative amount in the younger more metabolically active animals and hence growth would be retarded to an equal or greater degree than in the older groups. Moreover, the younger test groups (23, 30 and 50-day-old series) as they grow older presumably decrease in metabolic activity, yet they fail to exhibit any decrease in percentage rate of growth different from that which normally occurs with age (2). This they would be expected to do if the interpretation was adequate. Finally, it might be said, as has been done in earlier papers, that the reaction is due to the progressive decrease with age in the growth capacity which is inherent in the organism as a collection of living cellular units, and that the urge to grow being weaker it is the more susceptible to blocking by adverse conditions. Such an entlechical interpretation is merely a begging of the question and only useful as a tentative point of view.

The interpretation that is acceptable is consistent with the facts. It of course differs from that given for the age reaction to thyroid deficiency because the primary disturbance is different. It is, however, consistent with the idea developed in the preceding paper (2) that the growth retardation of parathyroid deficiency is immediately largely conditioned by a situation essentially the same as that existing in thyroid deficiency (e. g. a decrease in the amount of materials available for growth); and with the complementary idea that the mechanism of growth adjustment to the two types of glandular deficiency is also essentially the same.

That puberty is a factor conditioning the degree of growth retardation to parathyroid deficiency in the males in body weight and length, and in the females in body weight is shown on charts 1 and 2 by the abrupt decrease which occurs in the relative per cent growth of the tests at this time. That this

effect is apparently restricted in the males to this period, following which the retardation becomes approximately the same as before, is an inexplicable anomaly which, however, does not detract from the validity of the generalization. The significance of the phenomenon has been discussed elsewhere (2). Attention is called to it here as it will be in future papers in order to attest its ubiquitousness. That it is real and differential in its influence will be shown.

#### SEX DIFFERENCES

Now the direction of the sex difference in degree of growth retardation in body weight, body length and tail length, due to thyroid deficiency, is correlated with the direction of sex difference in normal growth rate and on the same course as that which occurs with age. That is to say, just as the degree of retardation is greater the less the rate of normal growth on age; so is the degree of retardation greater in the females of normal lesser rate of growth than the males. This is what is to be expected if the interpretation of the age differences is well founded. Its occurrence is, therefore, consistent with and confirmatory of the conception (2).

Parathyroid deficiency, on the other hand, results in a greater growth retardation in body weight, body length and tail length in the male than in the female. This reversal of direction of sex difference is not a breach in the validity of the interpretation, as it might be considered at first sight.

The sex difference in degree of retardation is conceivably due to the sex difference in the degree to which the nutrient level is reduced. This is directly due to the sex difference in sensitivity to the toxemia of the parathyroid deficiency. That is to say, in the case of parathyroid removal, growth retardation is secondary to a toxemia. Sex specific factors determine the primary response from which the subsequent growth reaction is conditioned. In the case of thyroid removal, however, this supplementary influence is absent and the sex difference in response is determined by the inherent sex difference in normal growth rate and the relation of thyroid activity thereto.

On the basis of what has gone before it would be expected that the puberty effect would be more marked in the sex which is the more sensitive to the particular glandular deficiency. Such is found to be the case as can be seen from chart 1. The

change in degree of growth retardation occasioned by thyroid removal at the attainment of sexual maturity is more marked in body weight and body length in the females than in the males. In the parathyroidless groups, on the other hand, it is the males that are more seriously affected, the females showing little if any alteration from the normal progressive decrease with age. The consistency of these interrelations with the basic assumptions is gratifying.

#### BODY WEIGHT, BODY LENGTH AND TAIL LENGTH DIFFERENCES

The values in table 2 show that the relative degree of growth retardation in body weight, body length and tail length subsequent to glandular removal, bears no consistent relation to the relative degree of normal growth. This is what is to be expected since the growth processes concerned are presumably qualitatively as well as quantitatively different (9).

From chart 2 it is seen that growth in body weight is consistently more retarded by both types of glandular deficiency than is growth in body length and tail length. As a result the test animal becomes more rangy than the normal. This shift in bodily proportions is like that which occurs in conditions of defective nutrition (10). The similarity indicates that the interpretation of the growth response to the glandular defects in terms of decrease in materials available for growth is well taken.

In a previous paper (11) the assumption was made that growth in body weight is more representative of growth by increase in cell mass, while growth in body (or tail) length is more representative of growth by increase in cell number. A strict delimitation of the two phases is obviously not intended in this broad generalization. Evidence that growth of the axial skeleton of the albino rat by increase in cell number persists for a considerable time after birth, even up to the age when body growth in weight is almost exclusively a matter of increments in cell mass is had from a recent paper by Strong (12). Hence assumption is not inconsistent with observation.

On the basis of this differentiation the conclusion was drawn that growth by increase in cell mass is more sensitive to inhibition by thyroid and parathyroid deficiency than is growth by increase in cell number. The analysis given in the preceding paper (2) and the observations reported by Jackson (10) sub-

stantiate and extend the deduction, respectively, so that the following biological principle can be stated: *Growth by increase in cell mass is more sensitive to inhibition by a diminution in the materials available for growth, than is growth by increase in cell number.* An expansion of the concept would be interesting but this is hardly the place therefor.

There is a very evident tendency for growth in tail length to be more retarded than growth in body length by thyroid deficiency. On the other hand growth in body length tends to be more retarded than growth in tail length by parathyroid deficiency.

This difference in the direction of difference might seem to be a stumbling block to the general validity of the growth retardation were it not for the fact that we are here dealing with structures, important components of which are peculiarly related to a phase of metabolism in direct relation to an apparently specific function of one of the glands being studied. I refer to the vertebrae in their relation, as bones, to calcium metabolism and the function of the parathyroids in its relation to the same process. Under conditions of parathyroid deficiency in which, on a retardation due to lowering of the general nutrient level there is superimposed a retardation (specific for bone growth) due to a specific diminution of available calcium, it is not to be expected that the relative growth of the vertebrae of the tail as compared with those of the body would be the same either in degree or in direction as under conditions where the specific defect of specific importance to bone growth is lacking or at least much less marked as is the case in thyroid deficiency (13). It is not to be expected because each group of vertebrae obviously has its own distinctive type of metabolism with its own relation to growth, and hence its own type of response to the specific and non-specific metabolic defect which in turn must participate in the determination of the relative degree of response to the different conditions. This phase has already been discussed as noted earlier (9).

#### DIFFERENCES IN RESPONSE TO THE TWO TYPES OF GLANDULAR DEFICIENCY

From chart 3 it is seen that the degree of retardation of growth in body weight, body length and tail length is generally

less in parathyroid than in thyroid deficiency. It is less in the former than in the latter because the decrease in material available for growth is less. It must not be overlooked, however, that this decrease is a consequence of a distortion of cell activity, in the one case by a toxemia, in the other by a lowering of the metabolic level, and that the former is presumably largely mediated through a specific action on the nervous system and is hence restricted, while the latter is general and on the basic processes common to all living cells.

Now it has been pointed out that the degree of retardation increases with the age at which the glandular deficiency is initiated. It will be noted from chart 3 that the extent of this decrease is greater in the case of thyroid than in the case of parathyroid deficiency. This relation is in accord with the interpretation of the age difference in degree of response and is another example of the interdigititation of observation and theory.

The influence of puberty in bringing out a differential response is shown in the body weight and body length values. The effect is more marked in the males than in the females.

In general the difference in degree of response to the two types of glandular deficiency is greater in the female than in the male. This is because the female is less retarded than the male by parathyroid deficiency and tends to be more retarded by thyroid deficiency. This difference has been interpreted in an earlier paragraph. The difference is more marked in the tail length relations, which fact is consistent with the idea of Przibram (14) that tail length is a facultative tertiary sex characteristic in the rat. If the hypothesis is correct it is of importance to students of the secretory organs.

#### SUMMARY

In the foregoing pages I have pointed out and interpreted the salient sex and systemic similarities and differences in growth response to thyroid and parathyroid deficiency initiated at different stages of development in the life of the albino rat in so far as growth in body weight, body length and tail length is concerned. The agreement of the findings with the principles developed from a study of the course of growth of these same animals is good, and an indication of their essential validity.

The following are the significant points from which the interpretations and conclusions found in the text are derived:

1. The older the animal at the time of the initiation of the glandular deficiency the greater the subsequent retardation of growth in body weight, body length and tail length.

2. Puberty is a significant factor in the determination of the growth response to thyroid and parathyroid deficiency.

3. Growth of the male is less dependent on the functions mediated by the thyroid than is growth in the female.

4. Growth of the male is more retarded by parathyroid deficiency than is that of the female.

5. Growth in body weight is more retarded than growth in body length or tail length.

6. Growth is more retarded by thyroid than by parathyroid deficiency.

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STUDIES ON THE OESTROUS CYCLE IN THE RAT.  
II. THE EFFECT OF THYROPARATHYROIDECTOMY  
AND PARATHYROIDECTOMY

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The effect of thyroidectomy on the oestrous cycle in the female albino rat was reported in a previous paper (Lee, 1925). The length and character of the oestrous cycle, as determined by the vaginal smear method, was used as an index of ovarian activity, thus affording what is believed to be an accurate objective method of studying the supposed intimate relationship between the thyroid and ovary. The effect obtained was an average lengthening of the cycles in thyroidectomized animals of about one day over cycles in normal controls (5.9 and 4.8 days respectively). This lengthening of the oestral rhythm is conceivably due to the loss of the direct stimulating influence of the thyroid on the ovary, or more likely to the lowering of the general level of metabolism in the animal.

Using reproductive ability and the growth of the reproductive organs as an index of the inter-relationship of thyroid and ovary, Hammett (1922, b; 1924) has concluded that parathyroidectomy and thyroparathyroidectomy have no direct effect on the reproductive system, but an indirect one due to the lowering of the metabolic level of the organism and resulting in a condition of partial physiological inanition. That ovarian activity is closely conditioned by the general well-being of the animal is a fact reported by several workers (Evans and Bishop, 1922; Papanicolaou and Stockard, 1920) and attested by numerous experiences in this laboratory. Any condition of loss of weight, infection, undernutrition, crowding of animals in small cages, or extreme variations in temperature, is quickly reflected in a prolonged dioestrus interval in the oestrous cycle.

The use of the length and character of the oestrous cycle as an index of ovarian activity is regarded as being well adapted to these particular problems. The vaginal smear method of

following the cycle in the rat, developed by Stockard and Papanicolaou (1917) and by Long and Evans (1922), affords an easy means of following cycle after cycle of ovarian activity without interfering with the process to any significant extent. For example, in the three series of 57 rats reported in this paper, 1836 cycles, involving a total of 9904 days or more than 27 years, were followed in a course of six months. Since any method of studying inter-relationships of endocrine glands is essentially a statistical one, the advantages of a method giving a large mass of data are apparent at once. To obtain an equivalent number of data by the use of reproductive ability as an index, for example, would require either many times the number of animals, or that the observations be carried on over a period of years.

#### MATERIAL AND METHODS

Eighty-four female albino rats of from 100 to 150 days were used in these series. Twenty-three of these served as controls, and were also used as controls for the thyroidectomized series reported upon previously. Parathyroidectomy was performed upon twenty animals and thyroparathyroidectomy upon forty-one others. Of these, thirteen rats died after the operation, seven developed poor health during the course of the experiment and were discarded, while seven others were found at autopsy or biopsy to have regenerated some thyroid or parathyroid tissue. These also were discarded from the groups. Five of the control series were subjected to a sham operation to determine the effect of trauma on the cycles. Later in the experiment the incisor teeth of these five animals were kept short, as a check on a similar condition in the parathyroidectomized animals.

The environmental conditions, food, housing arrangements, etc., are described in detail in the previous paper and need not be repeated here. It should be emphasized possibly that the ration was rich in calcium (1.5%  $\text{CaCO}_3$ ).

In the removal of the thyroids and parathyroids the following technie was used. The animal was maintained under ether anesthesia and tied out, back down, on a small board under a binocular microscope. After exposure of the tissues in the neck,

fine silk ligatures were placed around the vessels entering each thyroid lobe at the anterior and posterior ends, care being taken that all of the thyroid and parathyroid tissue lay between the two ligatures. The mass of thyroid and parathyroid tissue was then grasped by fine forceps and carefully teased out with a flexible needle. Histological examination was made of all tissues removed, to make sure that both parathyroids were actually ablated. One animal in which the extirpated thyroids contained only one parathyroid was discarded from this series and placed in the thyroidectomized series.

In the removal of the parathyroids alone, essentially the same general technic was followed except that ligatures were placed only at the anterior poles of the thyroids. From each lobe a small amount of thyroid tissue (not over one-fourth of the gland) containing the parathyroid was then removed. In some cases the parathyroid was so prominent that it could be easily cut cleanly away from the surrounding thyroid. In actual practice it was not decided which glands of a particular animal were to be removed until the neck tissues were exposed. Then in case the parathyroids were plainly visible under the capsule at the anterior poles of the thyroids, they alone were removed and the animal was placed in the parathyroidectomized series. In case the parathyroids were embedded deeply in the thyroid and not visible from the surface, both glands were removed and the animal was placed in the thyroparathyroidectomized series.

The mortality from the operations was fairly low, 20 per cent of the thyroparathyroidectomized, and 20 per cent of the parathyroidectomized animals dying. It has been shown by various workers (Boothby, 1921; Islein, 1908) that complete parathyroidectomy is not always fatal in the rat, and Hammatt (1921) has shown that the extent to which the animals have been "gentled" has much to do with the percentage of survivals.

At the end of the observation period all of the experimental animals were autopsied or biopsied, as a check on the completeness of the operation. From the thyroparathyroidectomized series all suspected tissues was removed and sectioned. Of the thirty animals, three showed some regeneration of thyroid tissue and one showed some parathyroid tissue which had either not been removed or which had regenerated. These rats were dis-

TABLE 1  
*Show ing Lengths of Oestrous Cycles, in Order of Occurrence, in Control Series*

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES		TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
	275	276			
275	5,6,4,5,5,4,4,5,5,7,6,4,6,5,6,4,5,5,4,4,5,5,4,5,6,5,5,5,4,5,4,5,4,4,5,5,4,5,5,5,5,.....	52	249	4.8	4.8
276	6,5,5,6,5,5,4,4,5,6,5,4,4,5,6,5,4,5,5,4,5,5,4,5,5,6,5,4,5,5,5,4,5,5,5,5,4,5,5,5,.....	49	240	4.9	4.9
222	5,6,5,4,5,5,6,4,4,5,4,5,6,4,5,5,4,5,6,5,5,5,4,4,5,4,5,5,4,6,4,5,5,4,5,5,4,5,5,4,.....	51	246	4.8	4.8
284	5,6,4,5,6,5,4,5,6,5,5,4,4,6,7,5,5,6,5,5,5,4,5,5,5,4,5,5,4,5,6,5,4,5,4,5,6,4,5,.....	49	245	5.0	5.0
287	5,4,6,4,5,6,5,4,5,4,4,5,5,6,4,5,5,5,5,4,5,5,6,7,5,5,5,4,5,5,4,5,5,5,4,5,5,5,.....	51	248	4.9	4.9
288	5,4,5,5,4,6,5,5,4,5,5,5,5,5,4,4,5,5,5,5,4,5,5,5,4,5,6,4,5,4,5,6,5,5,4,5,5,5,6,5,4,5,.....	52	250	4.8	4.8
297	5,6,5,6,4,6,6,5,4,5,5,5,5,6,4,4,5,5,4,5,5,4,5,5,5,4,5,5,5,4,5,5,5,4,4,5,.....	50	241	4.8	4.8
298	4,5,5,4,5,5,5,4,4,5,5,4,4,5,5,4,5,5,4,5,5,6,5,5,5,5,4,5,5,5,5,6,4,5,4,5,5,5,4,5,6,.....	51	245	4.8	4.8
413	4,4,5,6,5,4,5,6,4,5,4,4,4,5,5,5,5,5,5,4,5,5,5,4,5,5,5,4,5,4,4,5,5,5,6,5,5,5,5,.....	51	244	4.8	4.8
564	5,4,5,5,5,4,4,6,4,5,5,5,5,5,6,5,5,5,7,4,4,5,4,5,5,5,5,6,4,5,4,5,5,4,5,5,4,5,5,4,.....	50	243	4.9	4.9
565	5,6,6,5,7,5,4,5,6,4,5,4,5,5,5,4,5,4,5,5,6,5,5,5,5,5,4,5,4,5,5,5,5,5,4,5,5,6,.....	49	243	4.9	4.9
566	6,4,6,6,5,5,5,4,5,5,5,4,5,5,4,5,5,5,4,5,5,5,4,5,5,5,4,5,5,5,4,5,5,5,4,4,5,5,5,6,5,.....	51	248	4.9	4.9
586	4,4,5,4,4,5,5,5,5,4,5,5,4,4,4,5,5,5,6,6,5,4,4,6,4,5,5,5,4,5,5,5,4,5,5,5,4,5,6,4,5,4,.....	52	246	4.7	4.7
587	5,5,5,5,4,5,5,5,4,4,4,5,5,5,5,4,5,5,5,4,5,5,4,5,5,4,5,6,4,5,4,5,5,6,4,5,4,5,6,4,5,5,.....	51	242	4.7	4.7
588	5,5,5,5,4,4,5,5,5,5,4,5,5,4,5,5,5,5,4,4,5,5,5,5,6,4,5,5,5,5,4,4,5,5,5,5,5,4,5,4,5,.....	51	245	4.8	4.8
	Average.....	760	3,675	....	....
	Standard deviation.....	..	50.7	245	4.8
					<u>+0.1</u>

carded from the series. From the parathyroidectomized animals all of the thyroid tissue left behind at the operation was removed and sectioned. In all of these cases there was abundant thyroid tissue present and in a few cases thyroid that had been left had apparently hypertrophied. In two cases some parathyroid tissue was found as small islands in the thyroid. These animals were discarded. Thus in the final series only those animals were included which were positively lacking the parathyroids or the thyroids and parathyroids, respectively.

In thirty-nine animals symptoms of parathyroid deficiency became apparent after the operation. The first symptom noted was the development of typical parathyroid tetany in twenty-one cases within two days after the removal of the glands. Eleven animals succumbed to the attacks, the remaining ten recovering and showing no further evidence of tetany. Tetany was not observed in twenty-seven animals, but it should be mentioned that they were under observation only a few hours each day. The second effect did not show until some time after the operation when, in most of the parathyroidectomized and in some of the thyroparathyroidectomized animals, the teeth began to show an overgrowth, becoming much longer, curved and curled as described by other observers (Hammett, 1922, a). In most cases the teeth also became brittle and soft, breaking easily at the level of the gum. As soon as this condition was noticed the teeth showing overgrowth were kept clipped to something like normal length. These rats showing abnormal teeth were often unable to gnaw or to eat hard food, and soft food (of the same composition as the baked ration of the other animals) had to be used. This ration was not always eaten readily and in some cases body weight was not maintained.

In order to determine just what effect this disturbance of the teeth and the subsequent partial inanition might have on the oestral cycles, the condition was imitated in the five traumatized control rats, which had completely recovered from the effects of the sham operation. The incisor teeth of these animals were clipped just above the gum once a week, and soft food was fed. Bodily growth and weight were not maintained and the oestral cycles became longer and more irregular, as may be seen from examination of Table 2.

TABLE 2  
*Showing Lengths of Oestrous Cycles in Traumatized Rats*

RAT NO.	(A). LENGTHS IN DAYS OF SUCCESSIVE CYCLES AFTER SHAM OPERATION	SUMMARY (A)		
		NO. OF CYCLES	NO. OF DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
347	(8), (9), 6, 5, 4, 5, 4, 4, 6, 5, 5, 4, 5, 4	12	57	4.8
232	(10), 4, 5, 5, 4, 4, 7, 5, 4, 4, 6, 5, 5, 5, 4	14	67	4.8
205	6, 5, 5, 6, 4, 5, 5, 4, 8, 4, 5, 5, 4	13	66	5.1
168	(9), 5, 7, 4, 6, 5, 4, 4, 4, 8, 4, 5, 5	12	61	5.1
242	(11), 6, 7, 4, 4, 5, 5, 3, 6, 5, 4, 5	11	54	4.9
	Totals	62	305	
	Average length of cycle (days)			4.9

RAT NO.	(B). LENGTHS OF CYCLES DURING PERIOD OF CLIPPING INCISOR TEETH	SUMMARY (B)		
		NO. OF CYCLES	NO. OF DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
347	5, 4, 6, 9, 7, 4, 6, 6, 5	9	52	5.7
232	4, 6, 5, 7, 5, 8, 4, 5	8	44	5.5
205	5, 9, 6, 5, 7, 6, 5, 5, 6	9	54	6.0
168	6, 4, 5, 7, 5, 4, 6, 8	8	45	5.6
242	5, 8, 7, 5, 6, 3, 8, 5	8	47	5.8
	Totals	42	242	
	Average length of cycle (days)			5.7

\* Parentheses ( ) around numbers indicate lengthened cycles immediately following operation. These figures were not used in the calculations

Daily determination of the stage of oestrous were made by the vaginal smear method, in the case of the control series from October to the following June, and in the case of the experimental animals from December to the following June. The experimental rats were operated upon in January, their oestral cycles from the time of puberty up to the time of removal of the glands having been normal in length and character.

#### OBSERVATIONS AND DISCUSSION

In the control series of fifteen animals the cycles were within normal limits in length and character throughout the period of observation, indicating that environmental conditions were favorable. The total average length of cycle in these controls over a period of eight months was 4.8 days, a figure which differs but slightly from that found by Long and Evans (1922) in their colony. For the details of the cycles in these rats see Table 1. Four of the five traumatized control animals showed lengthened cycles immediately after the operation, followed by a return to normal length. Later, after clipping of the teeth began, the cycles became somewhat longer and more irregular (see Table 2). In the three rats which showed regeneration of the thyroids there was a return to cycles of nearly the same length as those of the controls.

The thyroparathyroidectomized series after discarding all rats showing regeneration, consisted of twenty-six animals, all of which had shown cycles of average normal length (4.9 days) before operation. Nineteen of these animals showed a disturbance of the oestral rhythm immediately after the ablation of the glands, lasting from 9 to 35 days and involving one to three cycles (Table 3). This lengthening of the cycles is ascribed chiefly to operative injury and, in some cases, slight infection, since it is very similar to the condition in the traumatized control series. Seven of the parathyroidectomized rats showed a similar disturbance of the cycles after operation, although not so extensive as in these thyroparathyroidectomized animals. The trauma was undoubtedly more severe in this series from which both glands were removed, but there still remains the possibility that following thyroidectomy or thyroparathyroidectomy some endocrine adjustment may occur, and that only gradually as this adaptation takes place does the ovarian activ-

TABLE 3

Showing Lengths of Oestrous Cycles, in Order of Occurrence, in THYROPARATHYROIDECTOMIZED Rats

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF CYCLES DAYS
147	(15), 6, 9, 6, 6, 3, 4, 8, 5, 8, 4, 5, 6, 6, 7, 5, 6, 4, 8, 6, 8, 5, 7, 5, 6, 6, 7, 5	28	167	6.0
243	(5), (16), (10), 8, 7, 6, 5, 8, 7, 8, 7, 9, 5, 7, 7, 5, 5, 6, 6, 5, 5, 4, 6, 5, 6, 4, 4, 6, 5, 5, 7, 4, 5	32	188	5.9
248	6, 6, 11, 5, 4, 8, 5, 6, 5, 5, 8, 7, 7, 5, 5, 9, 5, 5, 7, 6, 4, 9, 6, 5, 5, 10, 6, 4, 6	29	180	6.2
495	(25), 5, 7, 5, 5, 4, 8, 4, 6, 5, 9, 5, 6, 6, 6, 6, 10, 5, 4, 6, 7, 6, 5, 6, 7, 6, 7, 6, 6, 5, 8	31	186	6.0
551	7, 4, 6, 5, 7, 5, 6, 6, 5, 4, 8, 6, 7, 5, 9, 4, 6, 5, 6, 8, 6, 5, 6, 5, 9, 4, 5, 6	28	165	5.9
554	(8), (14), 5, 4, 10, 6, 5, 7, 6, 7, 9, 4, 6, 6, 7, 5, 6, 9, 6, 5, 7, 5, 6, 6, 8, 7, 7, 6, 4, 5, 7, 5	30	186	6.2
562	(16), (9), (10), 6, 4, 6, 5, 6, 5, 7, 5, 6, 3, 6, 6, 6, 5, 7, 8, 5, 5, 4, 5, 7, 6, 6, 5, 6, 7, 8, 6	30	171	5.7
577	(14), 6, 6, 5, 6, 8, 7, 6, 5, 6, 7, 6, 8, 7, 6, 5, 6, 3, 6, 7, 6, 8, 4, 6	29	178	6.1
598	(16), 8, 5, 9, 6, 5, 5, 7, 4, 5, 6, 8, 6, 6, 5, 4, 9, 7, 6, 6, 7, 6, 8, 5, 6, 7, 8, 7, 5	28	174	6.2
610	(21), 7, 4, 8, 7, 5, 6, 5, 7, 7, 4, 5, 6, 6, 5, 6, 7, 5, 8, 5, 7, 4, 6, 5, 6, 4, 6, 5	29	166	5.7
624	(9), (13), 5, 7, 7, 10, 6, 4, 4, 5, 6, 7, 4, 7, 6, 7, 5, 8, 7, 8, 5, 7, 6	23	144	6.3
767	(19), 7, 4, 6, 9, 7, 7, 9, 6, 5, 6, 5, 6, 5, 6, 5, 6, 7, 3, 9, 4, 5, 6, 8, 7	27	164	6.1
768	7, 8, 7, 5, 6, 6, 7, 7, 8, 5, 7, 6, 6, 7, 8, 6, 6, 5, 8, 5, 6, 5, 7, 5, 7, 6	28	180	6.4
770	6, 5, 9, 8, 8, 1, 5, 7, 6, 8, 6, 7, 4, 6, 5, 8, 6, 5, 4, 6, 7, 6, 5, 9, 5, 6, 4, 6	28	171	6.1
780	(11), 7, 5, 6, 7, 4, 5, 8, 5, 5, 9, 4, 6, 5, 5, 7, 6, 8, 6, 4, 5, 7, 6, 5, 8, 6, 5, 5, 6	28	165	5.9
790	(9), (15), 8, 7, 4, 6, 5, 10, 6, 13, 7, 8, 5, 6, 9, 8, 7, 6, 5, 6, 9, 7	21	148	7.0

TABLE 3 (Continued)

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF CYCLES DAYS
853	(10),7,6,7,7,1,7,10,7,5,6,6,6,5,7,6,8,5,6,6,6,4,6,7,7,6,5	27	168	6.2
855	8,9,7,4,5,6,8,5,4,7,9,6,7,6,7,6,4,8,6,6,8,6	24	153	6.1
856	(14),8,6,4,7,9,6,4,6,5,7,5,8,5,6,7,5,7,6,8,5,6,4,5,6,7	26	157	6.0
857	(9),7,6,6,1,6,8,6,8,5,7,5,4,1,6,5,3,6,5,9,5,1,5,6,7,1,7,6,6,7	29	167	5.7
858	(10),4,8,6,8,5,6,5,1,8,5,7,5,6,6,5,7,5,7,6,8,1,5,5,1,8,6	25	118	5.9
859	7,6,5,6,5,7,9,6,4,5,7,5,7,6,6,8,4,6,4,7,6,0,5,7,6	26	154	5.9
863	(21),(11),7,5,5,4,6,6,7,6,5,5,1,6,5,6,5,0,5,6,6,0,6,6,6,7,6,5,8,7,6,6,5	31	178	5.7
870	(12),(11),(9),7,5,6,5,3,5,6,1,6,5,6,5,4,1,6,5,6,5,5,4,7,6,5,7,4	26	136	5.2
876	7,5,6,6,7,4,5,6,8,5,7,6,6,7,6,5,8,4,5,6,5,5,6,7	26	152	5.8
877	(12),7,8,4,6,5,6,6,4,5,8,5,5,9,5,6,7,1,6,5,7,7,6,5,6,7	25	149	5.9
	Total <sup>a</sup>	714	4295	
	Average length of cycle		.. .	6.0
	Standard deviation		.. ..	$\pm 0.3$
	Coefficient of variation		.. ..	5.0

\* For explanation of symbols see Table 2.

TABLE 4  
Showing Lengths of Oestrous Cycles, in Order of Occurrence, in PARATHYROIDECTOMIZED Rats

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
				.....
187	*(12), (9), 5, 6, 6, 5, 5, 8, 7, 4, 5, 5, 4, 4, 5, 5, 6, 5, 6, 6, 4, 5, .....	21	111	5.3
235	7, 4, 5, 4, 5, 5, 9, 6, 5, 8, 6, 5, 5, 4, 4, 5, 4, 5, 6, 7, 6, 5, 8, 5, .....	26	143	5.5
255	6, 6, 5, 4, 5, 4, 5, 6, 6, 5, 4, 4, 4, 5, 7, 9, 6, 4, 4, 5, 5, 4, 4, 6, 6, 5, 6, .....	27	141	5.3
278	(13), 6, 6, 4, 4, 5, 6, 9, 4, 5, 6, 6, 5, 5, 4, 5, 4, 4, 5, 10, 6, 5, 5, .....	23	124	5.4
290	6, 5, 5, 4, 7, 10, 6, 4, 4, 5, 4, 5, 6, 6, 5, 5, 5, 8, 7, 5, 5, 4, 4, 6, 5, .....	25	136	5.4
299	(10), 5, 5, 6, 4, 5, 5, 4, 11, 8, 6, 6, 5, 4, 4, 5, 4, 4, 6, 7, 5, 6, 5, .....	23	125	5.5
497	(7), (15), 7, 6, 6, 5, 5, 6, 4, 4, 5, 6, 5, 5, 9, 8, 4, 4, 3, 6, 5, 5, 4, .....	22	116	5.3
579	6, 5, 5, 11, 9, 4, 5, 5, 7, 5, 4, 4, 4, 6, 4, 5, 5, 7, 4, 4, 5, 6, 7, 5, .....	24	132	5.5
782	(9), (14), 8, 6, 6, 4, 4, 5, 5, 3, 5, 6, 4, 4, 7, 8, 6, 5, 5, 4, 4, 5, 7, .....	22	114	5.2
814	(18), 8, 6, 5, 5, 6, 4, 4, 5, 4, 8, 12, 6, 4, 4, 5, 6, 5, 5, 4, 5, 6, 8, .....	24	135	5.6
816	(14), (11), (9), 6, 6, 5, 5, 4, 4, 6, 5, 4, 6, 5, 5, 8, 5, 5, 4, 5, 7, 5, 5, .....	21	110	5.2
	Totals .....	258	1387	.....
	Average length of cycle (days) .....	..	..	5.4
	Standard deviation .....	..	..	$\pm 0.1$
	Coefficient of variation .....	..	..	1.9

\* For explanation of symbols see Table 2.

ity become adjusted to the new conditions. In the tables these abnormally long cycles are indicated by parentheses ( ), and were not used in the calculations. In seven cases there was only a slight arrest of the rhythm or none at all. The average length for the first three cycles of the whole series was 8.9 days.

Following this postoperative lengthening the oestral rhythm was reestablished, but the cycles became more irregular and somewhat longer on the average, as may be seen from Table 3. In all cases the dioestrus or rest period was the period which was lengthened, all of the other stages remaining well within the normal limits. In this series a total of 714 cycles was followed, giving a total average length of 6.0 days per cycle as against 4.8 days in the normal control series. This increase of 1.2 days or 25 per cent in the length of the cycle is quite consistent, and cannot be due to the prolonged cycles following the removal of the glands, since any of these exceeding nine days in length were not used in the calculations. As a further check the last fifteen cycles of each rat were considered, giving approximately the same average length.

In the eleven animals of the parathyroidectomized series a total of 258 cycles, exclusive of the lengthened ones following the operation, was followed, giving a total average length of 5.4 days or an increase of 12 per cent over the length of cycles in the normal controls. The same general considerations apply here as in the thyroparathyroidectomized series. The lengthening of the cycles again was consistent, the average of the last fifteen cycles of all rats giving approximately the same figure as the total average.

This lengthening of the oestrous cycles after thyroparathyroidectomy and parathyroidectomy is subject to the same possible explanations as is the lengthening after thyroidectomy. It is believed, however, that the evidence is stronger for the view that the effect is due to a disturbance of the general well-being of the animal and a lowering of the general bodily metabolism, rather than to the loss of any specific stimulatory effect of the thyroid on the ovary. The case of the parathyroidectomized animals strongly supports this view. It is rather difficult to imagine, and there is no evidence for, any direct causal relationship between parathyroid and ovary, yet there

was an average increase of 12 per cent in the length of the cycles after the removal of the parathyroids. In view of the rather serious effects of total thyroparathyroidectomy, or parathyroidectomy, such a disturbance might well be expected. These effects include the lowering of the general metabolic level; a decreased resistance to infection; disturbance of calcium metabolism, especially noticeable in the teeth; the lessened intake of food; and the resultant slowing of bodily growth, all of which are conditions that are usually reflected in prolonged oestral cycles. That the lengthening may be entirely explained by these disturbed conditions is indicated by the 18 per cent increase in length of the cycles of the controls whose teeth were kept short in imitation of the condition in the parathyroidectomized animals.

It is worthy of note that in the thyroparathyroidectomized series, the effects of thyroidectomy and of parathyroidectomy here combined in the same animals, seem to be additive. These animals show an average length of cycle of 6.0 days, as compared with 5.8 days in the thyroidectomized and 5.4 days in the parathyroidectomized series. This additive effect is easy of explanation on the basis of a disturbance in general metabolism and well-being, but is difficult to explain otherwise. If it is due to a direct, specific effect, then the specific effects of the thyroids and of the parathyroids on the ovary must be the same, which is highly improbable.

#### SUMMARY

1. Using the length and character of the oestrous cycle as an index of ovarian activity, a study was made of the effects of thyroparathyroidectomy and parathyroidectomy in two groups of albino rats.
2. The cycles following total thyroparathyroidectomy showed an average lengthening of 1.2 days, or 25 per cent over those in normal control animals.
3. Following parathyroidectomy alone there was an average lengthening of the cycles of 0.6 days or 12 per cent over those in controls.
4. These results are considered as being due to the effects of the removal of the glands on general bodily health and

metabolism, rather than as a direct specific effect on ovarian activity. Trauma in sham operations and inanition due to clipping of incisor teeth gave similar results in control animals.

5. The effects of thyroideectomy and of parathyroideectomy on the oestrous cycles, seem to be additive when both operations are performed in the same animal.

It is a pleasure to acknowledge indebtedness to Professor R. G. Hoskins for generous advice and suggestions in regard to these studies.

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## STUDIES ON VIGOR. VII. THE FATIGABILITY OF CASTRATED RATS

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Studies on rats by the revolving cage method have shown that castration results in a marked decrease in voluntary activity. In one series of experiments (Hoskins, 1925) sixteen control and sixteen experimental animals were studied over a period of 120 days. From a group of about fifty young animals that had become accustomed to the apparatus sixteen pairs (mostly twins) were selected; these were well matched both as to weight and as to activity records over a preliminary period of 20 days. Then the more active of each pair was castrated, the age of the animal being about 70 days. Beginning at about the twelfth day, on the average, the activity of the castrated animals began to lag behind that of the controls. At the fiftieth day after operation, the activity of the control group was at its height, averaging approximately 15,000 yards a day, while that of the castrated group averaged about 3200 yards. At the end of 100 days the averages were about 6000 and 3100 yards, respectively. Numerous subsequent observations have confirmed these results. Directly or indirectly, therefore, the testes condition in an important way the spontaneous activity of the animals.

Available data offer little in the way of explanation of such findings. Some observers have reported a slight depression of basal metabolism, but others have failed to corroborate this (Lusk, 1925). Certainly the slight decreases of oxygen consumption noted by investigators who have obtained positive results could not explain a decrease in activity to only a fifth of the normal. Indeed, as Lusk suggests, the decrease of metabolism, if it occurs, is more likely the result than the cause of the sluggishness.

Several possible explanations suggest themselves. Perhaps the most plausible is that the general irritability of the nervous

system is depressed with resultant decrease in the number of "driving" impulses that reach the effectors. That the sensory organs themselves are depressed is not likely from what is known of their activity in eunuchs. In one human subject, well known to one of us, acuity seems to be unusually high. Numerous incidental observations of castrated rats in our colony also give the impression that there is no outstanding sensory factor involved. A study of central nervous irritability has been planned, but no instructive data have as yet been secured.

It was believed that the field could be narrowed somewhat by a quantitative study of the fatigability of nerve-muscle preparations, *in situ*. It was realized, however, that results of such a study would not be conclusive. If a depression were observed it might be due to lowered efficiency of the effectors or of the supportive functions, such as circulation, sugar mobilization or respiration. Conceivably peripheral degeneration of motor nerve fibres could also play a role.

#### METHODS

In the study herein reported male albino rats were used as subjects. The animals ranged in age from 170 to 337 days. In most instances litter controls were used. Most of these had been tested previously in revolving cages as earlier described. The animals were anesthetized with amyta<sup>\*</sup>, which was injected subcutaneously so that uniform and prolonged anesthesia could be obtained. The sciatic was laid bare, sectioned near the hip joint and adjusted in a Sherrington electrode. The skin was then sutured over the incision. A medial incision was made into the thigh; by blunt dissection the femur was exposed and fixed by means of a small modified Harvard femur clamp. The gastrocnemius muscle was isolated from its distal attachment and connected by a strong linen thread to a heavy type Harvard muscle recording lever.

The approximate absolute strength of the muscle was first determined, using single break shocks of a maximal faradic current as stimuli. In order to obviate fatigue this orienting study was confined to four trials of each muscle. An initial weight of 250 grams was attached and the nerve stimulated. Using the first reaction as a guide, lead weights of the estimated required

\*We are indebted to Eli Lilly & Co. of Indianapolis for a generous supply of amyta.

number were either added or removed, and the stimulus repeated. In practice it was found that the fourth trial was adequate to fix the limit rather accurately.

The muscle was then stimulated automatically at one second intervals by means of a faradic current, using make shocks only. The primary coil of a Harvard inductorium was connected with a battery of 6.2 volts, the current being made and broken by a chronograph every second, the contact being maintained throughout the interval. The secondary coil was fixed in the same position, 4 cm., throughout the series of experiments. The break stimuli were short circuited by means of a special device illustrated in Figure 1. From the binding posts of the secondary coil, two No. 28 cotton-covered magnet wires were led

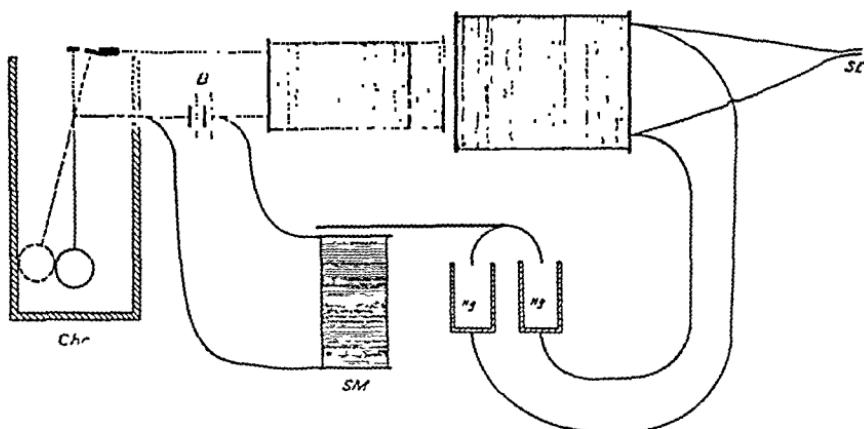


Figure 1. Short circuiting device. B., Battery connected with primary coil of Harvard inductorium. Chr., Automatic circuit breaker. S. M., Harvard signal magnet carrying curved metallic connector dipping into mercury cups, Hg. S. E., Stimulating electrode.

to the Sherrington electrodes, and two of No. 14 copper insulated wires were connected to two mercury cups. A signal magnet was connected with the battery. To the writing lever of the signal magnet an insulated U-shaped copper rider was attached. The signal magnet was so adjusted that when the current was made the rider was drawn down and into both mercury cups, and thus a short circuit was established. The lag of the signal magnet permitted the make current to reach the electrode and kept the circuit closed during the period of break. The chief practical difficulty encountered was in calibrating the diameter of the mercury cups to obtain the minimum surface tension effect. It was found necessary to connect

the primary of the inductorium and the signal magnet in parallel with the battery, and also to use a low resistance wire in the short circuiting device. By reversing the position of the signal magnet the make instead of the break shocks could have been eliminated.

The muscle was after-loaded with a weight of 50 grams and each contraction was registered by means of a slow-moving extension kymograph. The total amount of work was calculated by multiplying the summated height of the contractions by the weight lifted. No allowance was made for friction in the recording apparatus. At the conclusion of the experiment the muscle was dissected free and weighed.

#### OBSERVATIONS

In all, sixteen groups of two or three animals each were studied. These included 19 castrated and 18 control animals. Complete data as to work done were secured in 13 groups, comprising 15 experimental and 15 control animals. In 13 cases the total work done by the control animals was greater than that of the castrated, while in two instances the experimental animals surpassed the controls. The average amount of work of the controls in 12 groups in which complete data were secured was 107,924 gram-centimeters, while that of the castrates was 81,277 gram-centimeters. The ages at the time the final observations were made ranged from 170 to 331 days. The intervals between castration and ergograph tests varied between 95 and 277 days.

In view of the well marked difference in efficiency the question of weight and absolute strength of the muscles tested acquires a primary interest. In the 13 groups in which both total work and muscle weight were determined, this weight was greater in the castrated animals in all but two instances and the weights were equal in one of these. The averages in the 12 groups considered were respectively 2.10 and 1.86 grams. These differences were closely proportional to the total body weights which averaged 259 grams in the controls and 291 grams in the castrated animals. The ratios were 1:1.13 and 1:1.12, respectively; that is the muscle weight varied in the same proportion as the body weight.

The absolute strength of the muscle was greater in the con-

## FATIGABILITY AND CASTRATION

TABLE SHOWING RESULTS OF ERGOGRAPHIC EXPERIMENTS  
Gastrocnemius muscle after-loaded with weight of 50 grams.

Animal No.	Age in Days	Interval After Castration	Weight of Animal	Weight of Muscle	Absolute Strength Grams	Absolute Strength per Gram	Total Contraction Cm.	Work Gm. Cm.	Work Kgm. Cm. per Gm.	Daily Activity
159E	326	246	281	2 29	320	140	2550 5	127525	55.69	821
161C	326		312	2 10	330	157	3027 7	151385	72.09	4538
162C	326		276	1 88	270	144	1312 2	65610	34.89	3025
148E	332	251	356	2 42	325	134	4732	236650	97.79	2341
151E	337	252	302	2 05	380	185	3820	191000	93.17	1761
152C	337		248	1 92	380	198	6004	300200	156.32	4483
215C	331		290	2 35	260	111	1245	62250	26.47	1625
216E	331	265	265	1 85	260	138	927	46380	25.03	866
218C	331		285	2 25	220	98	1383	69150	30.73	2041
278C	310		248	1 75	220	125	398	20900	11.94	2058
280E	310	229	276	2 25	210	93	793	39650	17.62	900
193C	315		325	2 20	250	114	2315	15750	51.61	2158
197E	315	267	345	2 37	250	106	722	36100	15.23	2791
174C	324		335	2 05	340	166	1721	86050	41.97	8341
175E	326	277	365	2 32	340	147	810	40500	17.45	2258
993E	174	94	310	2 55	290	114	1022	51100	20.04	2314
992C	174		212	1 47	290	197	2360	118000	80.27	6801
2082E	177	97	280	1 75	240	137	1071	53850	30.77	4236
2078C	179		160	1 08	210	194	1602	80100	74.17	18018
2080E	177	97	280	1 80	280	155	1434	71700	39.83	4653
*920C	207		310		310			1806	90300	3300
*918E	207	184	320	2 80	270			962	48100	1119
*917E	207	184	300	2 75	270					751
989C	176		306	2 31	250	108	3826	191300	82.81	1856
988E	176	148	300	2 50	310	124	2940	122000	48.80	2340
1176E	170			2 05	310	151	792	39600	19.32	
1161C	170			1 80	280	155	1095	54750	30.42	
1177E	170		230	1 85	300	162	270	13500	7.29	
1162C	170		200	1 60	280	175	822	41100	25.69	
1178E	173		200	1 40	350	250	1368	68330	48.80	
1170C	175		180	1 40	300	214	3088	154400	110.30	
Averages Controls Experiments	260		259	1 86	279	153	21570	107924	59.26	5003
	249		291	2 10	294	145	16608	81277	38.34	2298
974E	193	95	220	1 50	350					5705
978C	194		180	1 30	320					7100
971E	209	114	225	2 10	310					607
969C	210		160	1 60	270					1044
928E	281	185		2 25	270		340	17000		686
929C	282			1 65	310					1903

\*Excluded from averages except absolute strength.

C—Control animals.

E—Experimental animals.

trols than in the experimental animals in 4 cases, less in 7 cases and equal in 5 cases. The averages in 12 groups were 279 grams in the controls and 294 grams in the castrates. When the absolute strength was calculated per gram of muscle, however, the results were as follows: controls greater in 10 and less in 4 cases. The averages in 12 groups were: controls 153, castrates 145, i. e., essentially equal.

The work done before complete fatigue was reached was greater in the control than in the experimental animals in 12

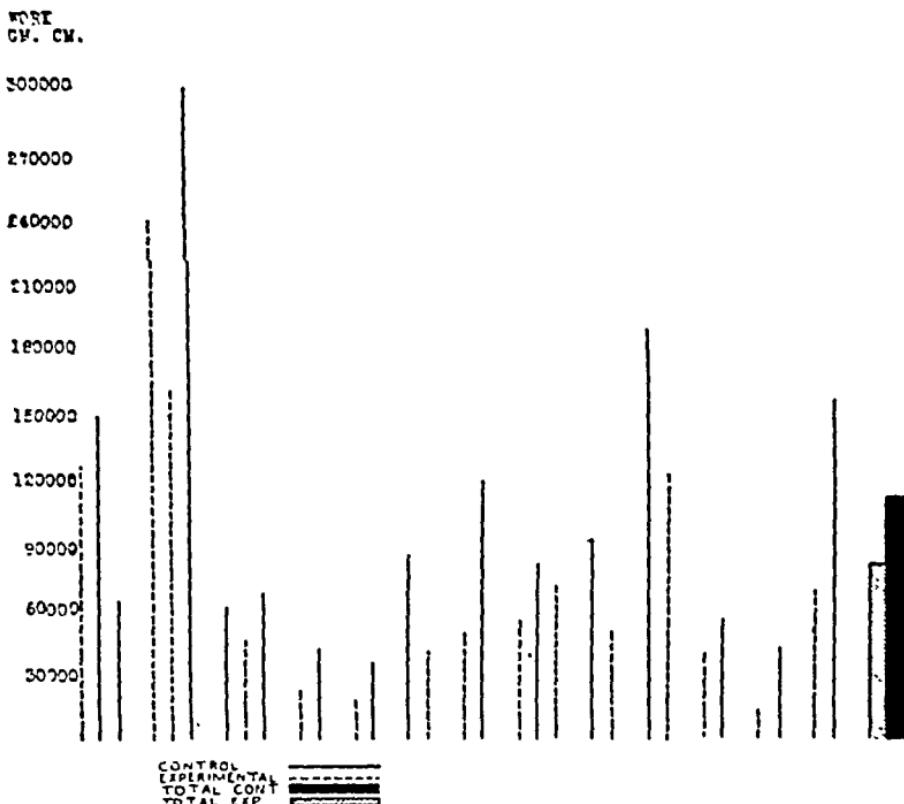


Figure 2. Work done by gastrocnemius muscles of castrated and normal rats. The muscles were stimulated through their motor nerves to the point of complete fatigue. They were after-loaded with 50 grams weight. In the graph for "total" read "average."

and less in 3 cases. The averages for 12 groups were: controls, 107,924 gram-centimeters; castrates, 81,277 gram-centimeters. Reduced to kilogram-centimeters of work per gram of muscle the results were: controls greater in 12 and less in 3 cases. The averages were: control, 59.26 kgm.cm. and experimental 38.34 kgm.cm. In Figure 2 the total work done is expressed graph-

ically. Even so considered, the advantage of the non-castrated animals is obvious. If the reduced data were plotted, the results would be even more striking.

In 10 of the 13 groups of animals activity cage records were available. These were averaged for the thirty days preceding the ergograph determinations. In all but two instances the controls were more active than the castrates. In most instances the differences were striking. The averages in 10 groups were: controls, 5003 revolutions; castrates, 2298 revolutions. Considering the fact that the controls in most cases were showing marked degrees of early senile depression, this difference is especially significant. If carried to extreme old age, no doubt the activity of both groups would become essentially equal and negligible. In a considerable number of senile animals that we have had under observation, the activity has amounted to less than 10 yards a day. Whether normal or castrated animals would attain this degree of sluggishness earlier is an interesting question that we have not studied.

#### DISCUSSION

Perhaps the most striking feature of the data at first glance is their marked lack of homogeneity. This might seem at once to indicate that they have little or no significance. Such a conclusion, however, is not justified. One of the surprising facts that has come out of the vigor studies we have made is that the spontaneous activity among litter mates varies widely. One animal is frequently several times as active as its twin, although both seem to be entirely healthy. For this reason the animals in such studies are always "typed" before any experimental procedures are begun. Hence, although there may be much variability as among groups, within the groups the initial activity is closely similar. In the experiments herein reported, the animals selected for castration were in general slightly more active than their controls. While there is considerable variability in this respect, in general the animals of a litter that are more vigorous in the earlier weeks continue to show this characteristic throughout the active period of their lives.

The experiments as a whole indicate that a considerable part of the sluggishness of castrated animals is to be ascribed to

lessened efficiency of the muscles. The only apparent escape from this conclusion would be to make the highly unlikely assumption that the motor nerves to the muscle are materially depressed in their irritability or, still less likely, in their conductivity. We know of no evidence that castration results in any such peripheral nerve changes.

Whether the decreased efficiency is due, however, to local changes in the muscle or to failure of supporting functions—circulatory, respiratory, or metabolic—the data give no evidence. The fact that the absolute strength of the muscles is not greatly different in the two groups suggests that the cause is to be sought elsewhere than in the tissues immediately involved. The investigation must obviously be extended to include a study of the effects of castration on the physiologic processes in general.

#### SUMMARY

1. A comparative study was made of the strength and fatigability of the gastrocnemius muscles of castrated and normal rats. The muscles were stimulated electrically through their motor nerves.

2. The weights of the individual muscles were greater in the castrated animals, but the absolute strength per gram of muscle averaged approximately the same in each group.

3. The proportion of gastrocnemius weight to total body weight averaged the same in each group.

4. The total work performed by the castrated animals was considerably less than that by the controls.

5. The increased fatigability of the castrated animals could be ascribed to lessened muscular efficiency, *per se*, but is more likely due to inadequacy of supporting functions, such as circulation or respiration.

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## Book Reviews

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INSULIN AND ITS USE IN DIABETES. J. J. R. Macleod and W. R. Campbell, 1925. The Williams & Wilkins Co., Baltimore.

The development of the insulin treatment of diabetes is an outstanding triumph of co-operation in research between the physiologist and the clinician. It is, therefore, altogether appropriate that volume six of Medicine Monographs, which deals with insulin and its use in the treatment of diabetes, should be the joint work of Prof. J. J. R. Macleod, physiologist, and Dr. W. R. Campbell, clinician, both of the University of Toronto. Dr. Macleod is responsible for the first sixty pages of the book. In the Introduction he briefly traces the history of the investigations which led up to the discovery of insulin by Banting and Best, and gives the results of a few of their experiments. This is followed by an account of the work of Collip in devising methods for the preparation and purification of insulin. An outline of the best methods in use at the present time for its quantity production is also given, and the nature of the numerous insulin-like substances that have been extracted from everything from yeast to clams is considered. Macleod discusses in a very illuminating way the results of the various experiments that have been performed on depancreatized dogs. He points out that insulin is necessary not only for the oxidation of glucose but also for the formation of glycogen, and suggests the possibility that the formation of glycogen may be a necessary step in the oxidation of carbohydrate. The fact that insulin reduces both the blood and the urine phosphates leads Macleod to the conclusion that glucose unites in some way with the inorganic phosphates of the blood. He points out that this view is supported by the findings of Embden and his collaborators, who have given evidence to show that a compound of phosphoric acid with a complex which yields lactic acid, undergoes decomposition during muscular work.

Several pages are devoted to a discussion of the present methods of both the physiological and clinical assay of insulin, and the shortcomings of these methods are clearly shown. The difficulty of establishing the glucose equivalent of a unit of insulin is also dwelt upon. The fact that in the early experiments depancreatized dogs treated with insulin invariably died, Macleod believes was due to the absorption of toxic substances produced by the action of intestinal bacteria upon imperfectly

digested proteins. This view is supported by the fact that in the later experiments in which the dogs were fed whole pancreas in order to supply them with trypsin, it was possible to keep them alive indefinitely.

The clinical section by Dr. Campbell includes a brief account of the early clinical experiments on insulin, an interesting discussion of the effects of insulin on metabolism, including the symptoms of hypoglycemia and the best method of avoiding this condition. This is followed by a thorough discussion of both the diagnosis and treatment of diabetes. Dr. Campbell feels that the patient should invariably be kept free from both glycosuria and hyperglycemia. This can be accomplished by the proper use of insulin and thus there is a possibility that the sugar tolerance of the patient may be increased. There is also a chapter on the dietetic treatment of the disease, which is supplemented by numerous recipes and tables of food equivalents. Full directions are given for making all the necessary blood and urine tests.

RATIONAL GLAND THERAPY FOR WOMEN PARTICULARLY IN RELATION TO MENSTRUATION. I. Wanless Dickson, 1926. H. K. Lewis & Co., Ltd., London. P. 96

This small book is one of a type the popularity of which seems to be fortunately on the wane. It consists largely of a summary of well known gynecologic data interspersed with a considerable amount of dubious interglandular endocrinology. This latter is cited without convincing evidence and in disregard of conflicting results in the literature. True to type, in lieu of scientific evidence, the book contains illustrative superficial case histories.

Whatever value it may have is not in its "rationality" but as a record of the empirical experience of the author with gland therapy. His results have apparently been more satisfactory than those of most gynecologists.

THE PRINCIPLES AND PRACTICE OF ENDOCRINE MEDICINE. William Nathaniel Berkeley, 1926. Lea and Febiger, Phila. and New York. P. 368.

It is unusual that an author so accurately reviews his own book as has Berkeley in this case. In the preface he states: "The title of this book is meant to be accurately descriptive. The practice of endocrine medicine is becoming daily a more important and fruitful field of medical labor; that such practice may be intelligent and scientific, an acquaintance with the principles of the subject is indispensable. A sincere effort has been made to simplify these principles. In respect of points

in doubt a short summary of arguments pro and con is given; but as far as possible controversial matter is abridged or omitted, unsubstantiated claims are mentioned with proper reserve.

"The book is primarily meant for doctors in active practice. The standpoint of the writer is that of the clinical practitioner—the physician in the presence of a patient with endocrine disorder. Symptoms and diagnosis are discussed at length and treatment is emphasized. Many details of treatment and dosage are given which have been heretofore inaccessible in print in any language.

"It is hoped that for general readers also the book may serve a useful purpose. It defines the actual scientific status of endocrinology today, and contradicts at least a few of the old wives' fables now told not only in popular but in pseudo-scientific literature as well.

"In view of the practical aim of the book, many topics of exclusively scientific interest have been only touched on. But in each case, for the benefit of scientists and laboratory men, the important references to modern sources of information have been fully given, so that further special inquiry may be facilitated."

These aims have been admirably achieved. The text is entertaining and thoroughly readable. The illustrations are well selected and the book is well printed.

Perhaps the best test of a book of this sort is its treatment of "pluriglandular disorders"—a topic that exercises an irresistible appeal to romancing in the case of many writers. While Berkeley's chapter is brief, it is highly sensible and instructive. As to therapeusis he says: "An effort must be made in a rough clinical way (smaller children can rarely be kept quiet enough for a basal metabolism test) to estimate the amount of each deficiency, and the dosage should be adjusted and readjusted for each patient. I deprecate very much the slovenly habit of giving indiscriminately the ready-made 'shotgun preparations' of a half dozen different hormones for sale in the shops. The pharmacists could not sell these formulas if the physicians did not prescribe them."

To those whose needs can be met in a book of 350 pages this volume can be highly recommended.

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# Abstract Department

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**Suprarenal transplantation.** Blodinger (J.), Klebanoff (H. E.) & Laurens (H.). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 22.

The left adrenal was removed from 15 dogs and a portion transplanted to some other site. Vascularization of the grafts was rapid. Living cells could not be demonstrated in them, however, after 34 days. When the intact right adrenal was removed all of the animals died, none surviving more than 4 days after the second operation, regardless of the age of the graft.—J. C. D.

**Adrenal cortex and somatic growth (Corticale surrenale e accrescimento corporeo).** Castaldi (L.), Arch. ital. di anat. e di embriol. (Firenze), 1925, 22, 297-36S.

The feeding of adrenal cortex of the ox to very young guinea-pigs favors the growth of the skeleton and the formation of muscle and fat. After development is complete feeding causes increase in weight of muscle and fat only. In respect to the action on the skeleton, the author believes it to be the direct action of certain unknown constituents of the adrenal cortex cells. Hence it is suggested that adrenal cortex be included with thyroid, hypophysis and thymus in treating conditions of undergrowth. The medullary substance should not be used, since it may prove harmful in long usage.—P. M. N.

**The adrenals in pulmonary tuberculosis (Il sondaggio potenziale fisico dei surreni nella tubercolosi polmonare).** Franco (P. M.), Folia med. (Napoli), 1925, 11, 321-345.

The author by a method of applying Röntgen ray stimulation to the adrenals shows that with the progress of pulmonary tuberculosis the resistance of the glands becomes less and their activity is decreased.—P. M. N.

**Investigation of the influence of the adrenals on the basic respiratory metabolism (Untersuchungen über den Einfluss der Nebenniere auf den respiratorischen Grundumsatz).** Nakayama (K.), Biochem. Ztschr. (Berl.), 1925, 155, 413-435.

A continuation of the author's preceding paper (Biochem. Ztschr., 1925, 155, 387), using substantially the same experimental methods. The author finds that extirpation of adrenals from rats

lowers the basal metabolism but slightly if at all. Similarly, the results of feeding experiments with levulose and cane sugar do not differ materially in normal and adrenalectomized animals. Finally, the addition of thyroid in the feeding experiments induces no substantial change from those experiments in which it was omitted. (The accessory adrenal tissue of the rat robs these experiments of sharp definition.—Abstracter.) The protocols of the experiments are given in full.—A. W. R.

**Suprarenal hemorrhage in the new-born.** Joseph (S.) & Raban (E.), *Zentralbl. f. Gynäk.* (Leipz.), 1925, **49**, 1; *Abst., Am. J. Dis. Child.*, **30**, 868-869.

Hemorrhages in the suprarenal glands as an accidental necropsy finding are frequently reported, but only a few cases have thus far been reported in which the hemorrhage was so extensive as to cause death. The authors report a case of a child born at term. The delivery was rather difficult, and the child was mildly asphyxiated but recovered without strenuous measures of resuscitation. Thirteen hours after delivery cyanosis appeared suddenly, and death occurred three hours later. At necropsy an extensive hemorrhage of the right suprarenal gland was found; there were no other findings, except a few small, superficial hemorrhages on the cerebral convexities. The authors conclude that venous congestion of the suprarenal, due to trauma during delivery, was followed thirteen hours later by hemorrhage, which finally ruptured the capsule and spread into the surrounding tissues.

**Studies in adrenal insufficiency.** Stewart (G. N.) & Rogoff (J. M.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1925, **23**, 190-195.

It was found that pregnant and lactating bitches survived removal of both adrenals for a much longer period than nonpregnant bitches or males. Hemorrhagic congestion of the gastro-intestinal mucosa occurred commonly in dogs dying of adrenal insufficiency (47 out of 52). Congestion of the pancreas occurred in 50 out of 53 cases in operated animals and twice out of 20 cases in normal dogs. Blood or blood pigment was found in the intestinal contents at autopsy in 50 out of 54 adrenalectomized dogs. This is not derived from food. Blood examinations showed a reduction in the relative volume of the serum per 100 c.c. of blood and a reduced conductivity of the serum, a few days before death in the operated animals.—J. C. D.

**Anatomy of the paraganglia in man (Zur Anatomie und Histologie der Nebenorgane der menschlichen sympathischen Nerven).** Iwanoff (G.), *Ztschr. f. Anat. u. Entwicklungs gesch.* (Berl.), 1925, **75**, 435-443.

The paraganglia of 149 specimens (4 embryos, 122 children

from 1 month to 13 years, 20 adults from 18 to 70 years, 2 dogs and 1 cat were examined). The number, form, size and position of these masses in the region of the abdominal aorta were recorded. Persistent and nonpersistent paraganglia were recognized. The nonpersistent showed a slow growth from 12 months to 18 months, after which degeneration took place and the structure completely disappeared by the 10th to 13th year. These apparently carry on the adrenogenital function up to the 12th to 18th months. After that time this function is carried on by the persistent chromaffin system. Vascular increase in the parenchyma, hyaline degeneration, decrease in the size and changes in the form, reaction and specific granulation of the chromaffin cells, growth of connective tissue and in lymphoid elements are all correlated more or less directly with age. Data are tabulated graphically.—A. T. R.

**Endocrine glands in pernicious anemia.** Mendershausen (A.), Klin. Wehnschr. (Berl.), 1925, 4, 2089-2136; Abst., J. Am. M. Ass., 85, 1924.

The author found the pituitary, pancreas, suprarenals and gonads practically normal in his thirteen cases of pernicious anemia. He found, however, in twelve of them changes in the thyroid gland (lymphocytic infiltrations with atrophy, occasionally increase in colloid).

**Thyroparathyroid and gonadal effects on sedimentation of the red corpuscles** (La reazione sedimentaria dei corpuscoli sanguigni suo comportamento negli stati tiroparatiroidici e genitalici). Vasaturo (A.), Folia med. (Napoli), 1925, 11, 241-263.

The velocity of sedimentation of the red corpuscles is decreased in hypothyroidism and increased in spontaneous or experimental hyperthyroidism. Parathyroidectomy increases sedimentation velocity. The male gonads have no influence.—P. M. N.

**Adiposis dolorosa (Dercum's diseases).** Winkelmann (N. W.) & Eckel (J. L.), J. Am. M. Ass. (Chicago), 1925, 85, 1935-1939; Abst., A. M. A.

Winkelmann and Eckel report one case and review briefly fifteen cases cited in the literature. The case described fits in with the generally recognized syndrome of Dercum's disease, showing the following features: (1) obesity (exclusive of face, hands and feet), weight 460 pounds (208 kg.), with painful masses; (2) ulcers on the legs and bullae on the fingers, and (3) asthenia. The pathologic findings were an adenoma of the anterior lobe of the pituitary body with enlargement of the sella turcica, an adenomatous hyperplasia of the left suprarenal, atrophy of the ovaries, and many recent hemorrhages in the thalamus and subthalamic regions. On

reviewing the necropsy findings of the fifteen cases in the literature, one is impressed by the pluriglandular involvement in most of the cases. In only two cases were there no definite changes in the ductless glands (Rome and Falta). Of the eleven patients in whom the pituitary body was examined, eight showed definite alterations; the thyroid was abnormal in twelve cases; the sex glands were pathologic in nine; the suprarenal in three, and the pancreas in two. The author's own case showed pituitary, suprarenal and ovarian pathologic changes. It is of interest from a clinical standpoint to note that the condition is five times more prevalent in the female and that most cases develop after the age of 35. The theory of endocrine malfunction seems best suited to explain the symptoms in this case.

**A peculiar (hermaphroditic ?) ovarian tumour.** Berner (O.), Arch. internat. méd. exper. (Liège), 1925, 1, 825-848.

In a hen that had ceased laying and had developed masculine characteristics, autopsy showed a small tumor in the small ovary. Microscopically the tumor proved to be a sort of adenoma containing columns of large clear cells and cell masses. In some places there were found tubules resembling immature tubuli seminiferi containing two sorts of cells, some large and clear, resembling spermatogonia and some, dark and small. There were also found some large ovum-like cells surrounded by smaller, flat cells resembling follicular epithelium. The tumor had originated from the germinal epithelium of the ovary, proliferating into it and forming cords and cell masses resembling the egg-tubes of Pflüger. The author regards these structures as probably sex-cells resulting from parallel conjugation of the chromosomes, but conclusive evidence was not found. The literature on "folliculomata" is discussed. Earlier investigators agree that these ovum-like bodies are not at all ova, but the author states that in accordance with modern opinion and experience of the plasticity of the sex-cells egg-cells may really develop in an ovarian tumor.—Author's Abst.

**Effect of injections of liquor folliculi (Effets de l'injection d'extrait de liquide folliculaire chez les femelles impuberess).** Brouha (L.) & Simonnet (H.), Compt. rend. Soc. de biol. (Par.), 1925, 93, 489-491; Abst., Physiol. Absts., 10, 478.

The extract from liquor folliculi of the mare, obtained by successive treatment with alcohol, petroleum ether, and acetone, was dissolved in olive oil and injected into rats. Sexually immature animals were used and the changes produced in the vaginal secretion followed. Certain animals were killed at various stages and examined. Injection causes a cycle resembling normal oestrus. There are distinct hypertrophic changes in the uterus, but none in ovaries or mammary glands.

Effects of the injection of extracts of follicular fluid into sexually mature females. Brouha (L) & Simonet (H.), Compt. rend., soc. de Biol. (Par.), 1925, 93, 557-558,

Continued daily injections of follicular extract into normal females (rats) lengthen the period of oestrous but do not suppress the periodic appearance of leucocytes in the vaginal smear. Injections during the last two or three days of gestation have no effect upon the normal course of pregnancy. Injections during lactation induce oestrus without apparent modification of mammary secretion. More hormone than is needed to induce the reaction in the spayed adult is required for the normal immature female.—E. Allen.

The presence of the feminine sexual lipoid in bird eggs and in the ovaries of fish. Fellner (O. O.), Klin. Wchnschr. (Berl.), 1925, 4, 1651-1652; Chem. Abst., 19, 3496-3497.

Egg yolks and fish ovaries were subjected to a chemical process identical with that used for the preparation of the active mammalian ovarian lipoid. The product so obtained was then injected in the course of 8 days, into a 1 kg. rabbit, that had previously been deprived (operation) of 1 horn of its uterus. The animal was killed on the eighth day. The remaining horn of the uterus had enlarged to 11 times its original size under the influence of a lipoid extract from 30 eggs. An identical enlargement was obtained with the lipoid extract from 125 gr. of fish ovaries. The lipoid from 2 placentas produced a 16-fold enlargement in 8 days. The mammae were typically enlarged in every case. Histology is also given. The lipoid from 30 eggs is, therefore, equivalent in activity to more than 1 placenta or 90 corpora lutea. Some interesting deductions are made as follows: One egg contains as much active substance as 100 of the ordinary ovarian tablets and almost as much as 1 intravenous dose of ovarian lipoid. Eggs must have a tendency to augment the bleeding of puberty and menstruation and should be avoided at this time. The amenorrhea of war may have been partially due to a lack of eggs in the diet. Since ovarian extract produces a hypertrophy of the mammae but inhibits milk secretion, eggs should be advantageous during pregnancy and contraindicated during lactation. It is also interesting in this connection that both eggs and caviar have long been classed as aphrodisiacs by the general public.

The female sex hormone. Frank (R. T.), Kingery (H. M.) & Gustavson (R. G.), J. Am. M. Ass. (Chicago), 1925, 85, 1558-1559; Abst., A. M. A.

Experiments reported by Frank, Kingery and Gustavson not only indicate that puberty can be accelerated artificially by injection of the female sex hormone, but also that as soon as the thresh-

old is once passed, the ovaries, which appear to respond more slowly than the tubular system to the female sex hormone (after a short latent period), can function just as in the adult. No evidence of stimulation of ovogenesis and the new formation of ova could be obtained even after continued injection of the hormone (up to twelve days). Injection of the female sex hormone into immature female white rats in from three to five days causes opening of the canal and estrual phenomena (*pubertas praecox*), without the occurrence of ovulation. After a further interval of from five to seven days, the artificially produced puberty may be followed by spontaneous regular cyclical phenomena consequent to follicle ripening and ovulation. If the threshold of puberty is once crossed, sexual maturity may be maintained spontaneously in immature rats. These findings are said to indicate that puberty results from the elaboration, in sufficient amount, of the female sex hormone, and that the advent of puberty is not due to the removal of an inhibitory influence, such as might be exerted by one or more of the glands of internal secretion, such as the thymus or the pineal.

**Influence of the ligation of the seminal ducts on the internal secretion of the testicles.** Futakawa (M.), J. Okayama Med. Soc., 1925, 423, (April); Abst. Japan Med. World, 5, 300.

Experiments were made on albino rats. It was observed that ligating the seminal ducts of old animals led to earlier degeneration of testicles and earlier death than in control rats. In the experimental rats there developed an abnormally accelerated desire for sexual intercourse, which was remarkable, but passed away very soon.—R. G. H.

**Tumors and sex characteristics (Tumoren und Geschlechtscharaktere).** Halban (J.), Ztschr. f. Konstit. (Berl.), 1925, 11, 294-326.

After a consideration of numerous cases, mostly from the literature, it is concluded that neoplasms of the adrenals and sex glands may influence morphologically the sex characteristics. The influence of the pineal gland on sexual precocity is still uncertain.

—A. T. R.

**A case of retarded growth (Ein Fall von Kleinwuchs mit kongenitalen Bildungshemmungen).** Hammerschlag (E.), Ztschr. f. Konstit. (Berl.), 1925, 11, 744-753.

The physical status of a 16-year-old girl is given and the cause of retardation and endocrine involvement discussed. In addition to over weight and under height, there were bilateral congenital shortness of fourth and fifth fingers and third and fourth toes. After thyroid tablet feeding for four months, plumpness decreased and the child did better in school. The sex organs were infantile.—A. T. R.

Hormone of the ovarian cycle. Hart (C. P.), de Jongh, Laquer & Wijsenbeek, Deutsche med. Wehnschr. (Berl.), 1925, 51, 1700; Abst., J. Am. M. Ass., 85, 1679.

The authors confirm fully Allen and Doisy's results with the follicular fluid. Besides this, they were able to obtain a protein-free solution with the same effects on the castrated mice.

Disproportion of the extremities in a eunuchoid giant (Die Disproportion der Extremitäten bei eunuchoidem Hochwuchs). Henckel (K. O.), Ztschr. f. Konstit. (Berl.), 1925, 10, 577-580.

Physical measurements are given of a 23-year-old man 187.7 cm. long showing unusually long legs (105.9 cm.) and arms (85.6 cm.).—A. T. R.

The influence of the ovary on the absorption of the pubic bones of the pocket gopher, *Geomys busarius* (Shaw). Hisaw (F. L.), J. Exper. Zool. (Balt.), 1925, 42, 411-441.

The pubic bones of both males and females of this species are the same up to the time of sexual maturity. In the mature animal the male symphysis pubis is well developed, while in the female the two pubic bones are normally widely separated. The resorption of the pubic bones in females is accomplished by osteoclastic activity. Castrated control males did not lose their symphyses. Injection of ovarian extracts into both castrated and normal males caused the dissolution of the symphyses. Spayed females, however, may also lose their pubic symphyses. Grafts of testicular tissue into young spayed females prevent resorption of the pubic bones. The femurs are not affected by injections which apparently influence only the pubes.—E. Allen.

The influence of the male sex gland on the female. An experimental study to determine the sex ratio of the offspring. Kovacs (F.), Am. J. Obst. & Gyn. (St. Louis), 1925, 10, 527-544.

Attempts were made to influence the sex ratio of the offspring by the subcutaneous injection of fresh testicular substance into female albino rats. Each of six rats received in six injections a total equivalent of three-fourths of a testicle from young males. Matings were made at the beginning of the injections. A total of 49 offspring were produced, the ratio of males to females being 133:100 as against a normal ratio of 105.5:100. Five other animals received injections of testis tissue beginning eight days before, and continuing several days after, mating. A temporary sterility of from 3 to 11 weeks was produced. In 27 offspring from this series the ratio of males to females was 145:100. Of six females in which testes from young males were successfully transplanted

intraperitoneally, four animals gave birth to 21 young, the sex ratio of males to females being 250:100. The explanation is offered that in these cases there is a high mortality of female-producing ova and embryos. This is also indicated by the small number of young per litter, 5.2 as against 7 or 8 in the normal. As the writer states, the paucity of experimental animals in the series precludes "drawing far-reaching conclusions."—M. O. Lee.

**Effect of prepuberty castration on subsequent cancer inoculation.**

Murphy (J. B.), & Sturm (E.), J. Exper. M. (Balt.), 1925, 42, 155-161.

Male and female mice castrated during the first seven weeks of life and implanted with cancer at later periods of life show a resistance definitely higher than do intact animals of the same age. This increased refractiveness is evident at three months after the operation, but is more pronounced at eight months to a year. Even castration in early adult life seems to increase the refractory state to later cancer inoculation. On the other hand, adult mice inoculated within a week after castration show slight if any evidence of increased resistance.—Author's Abst.

**Testis and hypophysis (Keimdrüse und Hypophyse).** Nukariya (S.), Klin. Wchnschr. (Wien.), 1925, 4, 1307-1308; Abst., Physiol. Absts., 10, 422.

Histological observations on the effect of castration of male rats at various ages on the pituitary. A new type of cell is produced (illustrated), containing a large vacuole filled with colloid material. It has a diameter of 20 to 25 microns. These new cells are present a few weeks after castration, even in animals castrated when 1 to 2 months old. The changes in the pituitary are therefore not dependent on the maturity of the testis.

**Influence of partial extirpation of the thyroid and adrenals in the parents on the endocrine system of their offspring (Über den Einfluss experimenteller Schädigung von Schilddrüse und Nebenniere der Eltern auf das endokrine System der Nachkommenschaft).** Seitz (A.) & Leidenius (L.), Ztschr. f. Konstit. (Berl.), 1925, 10, 539-566.

These experiments were made on rabbits. The most constant results were an increase in the hypophysis to two and three times the normal size in the first litter following thyroidectomy in the parents and distinct enlargement of the thymus of the young after adrenalectomy in the parents.—A. T. R.

**On the influence of the placental extracts upon the female genital organs and other viscera.** Suzuki (S.), Journal Chiba Med Society, 1925, 3 (January); Abst., Japan Med. World, 5, 359.

The author observed that by the administration of placental extracts the thymus underwent atrophy, while the thyroid was hypertrophied. The uterus was hypertrophied, while the ovary had the follicles fully developed.

**The behavior of embryonic chick gonads when transplanted to embryonic chick hosts.** Willier (B. H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 26-30.

One group of chick gonads was transplanted at a stage before their sex could be determined (4 to 6 3/4 days of incubation). Another group was transferred after differentiation had taken place (7 to 13 days). The chicks were incubated 9 days and then examined. The grafts grew into right or left gonads according to the side from which they had been taken and into testes or ovaries according to their own potentialities regardless of the sex of host. The gonads of the host produced no abnormal changes nor variations in the development of grafts of the opposite sex. No evidence could be found of the grafted glands influencing the growth of the gonads of the host.—J. C. D.

**The action of x-rays against the testicles of the albino rat, together with the vital staining of the interstitial cells.** Yamakawa (H.), J. Toyko Med. Soc., 1925, 39 (May); Abst., Japan Med. World, 5, 297.

The author exposed the testicles of albino rats to various lengths of x-rays, ranging between 0.08-0.18 AE, and found that all sorts of the rays produced almost the same destructive action against the interstitial cells. If the equal amount of different qualities of the rays should be absorbed, the results would be the same pathological changes. The spermatozoa are destroyed first, the spermatids next, while the spermatocytes are most resistant of all. One skin unit of x-rays would completely destroy the testicular cells. Sertoli's cells have higher resistance than the other cells, even than the interstitial cells. The changes in the testicular tissues do not develop evenly, but locally. The changes involve both the nucleus and the protoplasm. Altmann's granules disappeared sooner than did the nucleus. By x-rays the destruction of sperm cells is more complete than by mechanical means, such as ligation of the seminal ducts, atrophies caused by diseases, transplantations, etc. The normal interstitial cells atrophied and disappeared completely after the exposure. They are hardly stainable by the vital staining method, but when they are atrophied they easily take vital staining, and present histiocytal changes.—R. G. H.

**The sella turcica.** Camp (J. D.), J. Am. M. Ass., (Balt.), 1926, 86, 164-167.

Observations based on anatomic specimens and roentgeno-

grams show the normal sella to vary in contour and size. Variations in contour may be classed into three types: the round, oval and flat, of which the oval type predominates in the adult. The average sella will measure 1.06 cm. and 0.81 cm. in the antero-posterior and vertical directions, respectively. Variations in the shape of the clinoid processes are numerous, and union between the anterior, middle and posterior clinoids, producing a bridged sella, occurs in about 5% of cases. Such an anatomic variation seems to be of no clinical significance. Pseudo-defects and apparent anomalies of structure are easily produced in a roentgenogram by faulty localizing technic. Pathologic conditions producing changes in the sella are numerous, and the differentiation of these changes as to cause is difficult. Owing to the characteristic deformity of the sella usually produced by each, the differentiation between an intrasellar and an extrasellar lesion is generally possible.—Author's Summary.

**Action of placental, ovarian, and luteinic extracts on female generative organs (Ricerche comparative intorno all' azione di estratti placentari, ovarici e corporuleinici sull' apparato sessuale femminile).** Ceresoli (A.), Atti d. Soc. lomb. di sc. med. e biol. (Milano), 1924, 13, 290-296; Abst., Physiol Abst., 10, 538.

Alcohol-ether, acetone, and other extracts of either the ovary or the corpus luteum have an action similar to that of placental extracts on the generative organs of young rabbits and guinea-pigs. The stimulating action of placental extracts, particularly on the muscular coats of the uterus, is considerably greater than that due to either ovarian or luteinic extracts.

**Pregnancy blindness and acromegalia (Schwangerschaftserblindung und Akromegalie).** Frankl (O.), Ztschr. f. Konstit. (Berl.), 1925, 11, 166-169.

The author describes a woman who became totally blind in the last months of pregnancy. A few weeks post-partum the features became acromegalic, although vision returned, indicating that although the hypophysis became smaller there persisted a physiological alteration in this organ sufficient to bring about the symptoms of acromegaly.—A. T. R.

**The activity of human pituitary extracts (Ueber die Wirksamkeit der Hinterlappensubstanz der menschlichen Hypophyse).** Lampe (W.), Wien. klin. Wehnschr. (Wien.), 1926, 39, 15-16.

Assays were made of extracts of hypophyses from 20 human subjects. It was found that the posterior lobes gave potent desiccated preparations as determined by experiments on urine secretion, blood pressure and uterine contractions. The content of active sub-

stance from one gland to another showed considerable variation. The extracts were found to be notably stable.—R. G. H.

**Action of pituitary extract on the uterus.** Rucker (M. P.), J. Am. M. Ass. (Chicago), 1925, 85, 1637-1639; Abst., A. M. A.

The author shows that the action of pituitary extract on the uterus is quite characteristic. It never gives contractions with periods of rest between, but always a continuous series of contractions with increase in intra-uterine pressure. This action was illustrated in a case of inevitable abortion in which the labor was induced in the fourth month with a number 3 Voorhees bag. The patient was given  $\frac{1}{4}$  grain (0.0162 gm.) of morphine and 1/150 grain of atrophen at 1:30 p. m. At 8 p. m. she was having painless contractions of the uterus that averaged 10 mm. Hg, at intervals of two minutes. She was given 5 minims (0.3 c.c.) of pituitary extract subcutaneously. Five minutes later there was a characteristic pituitary extract action. The contractions increased in height only very slightly, but were continuous one after another, without any period of rest. Twenty-two minutes elapsed before there was the slightest pause between contractions. The intra-uterine pressure was increased 6 mm. of Hg. The patient still felt no pain. In other words, here was a dose so small (considering the stage of pregnancy) that it caused no action clinically, and yet produced an incomplete tetanus of the uterus.

**Roentgen-ray treatment of pituitary tumor.** Towne (E. B.), Arch. Neurol & Psychiatry (Chicago), 1926, 15, 92-102.

Two cases are reported in which the visual fields and visual acuity returned to normal following cross-fire treatment with one-third of a maximum skin dose of roentgen-ray once a month. No recurrence has taken place up to the present time, three and one-fourth and two years after the treatments were started. In the first case, a partial external ophthalmoplegia disappeared promptly, and measurable decrease in the size of the large intracranial extension of the tumor was demonstrated by shifting of areas of calcification in roentgenograms taken before, and two and a half years after the institution of treatment. All adenomas of the pituitary gland should be followed by repeated perimetric examinations. Operation should be undertaken only if visual acuity and the fields do not improve. There is good reason to believe that when roentgen-ray treatment gives a favorable result the risk is less and the result more lasting than that of surgical treatment.

—Author's Summary.

**The action of insulin in the spasmophilia of infants.** Adam (A.), Klin. Wehnschr. (Wien.), 1925, 4, 1551-1552; Abst., Chem. Absts., 1925, 19, 3307.

Rickets and spasmophilia are due to a disturbance in carbohydrate metabolism. Assimilation metabolism, which is necessarily great in growing animals, is dependent upon maintenance metabolism, which is essentially a carbohydrate and fat combustion. Anything that reduces the latter will injure the former (vitamin deficiency, fever, infectious diseases, lack of nourishment) and tend to produce spasmophilia. Conversely, easily assimilable food (cod-liver oil) or irradiation with ultra-violet light tends to reduce spasmophilia because they enhance maintenance metabolism. Carbohydrate metabolism can be enhanced by increasing the concentration of glucose in the blood (diet rich in sugar, and demobilization of glycogen by injecting adrenaline or acid) and by facilitating its fixation to the body cells (insulin). Spasmophilics who have been treated with sugar, insulin and adrenaline show either a reduction or a complete cessation of symptoms. Details of treatment are given.

**The reduced sensitivity to insulin of rats and mice fed on a carbohydrate-free excess-fat diet.** Bainbridge (H. W.), *J. Physiol. (London)*, 1925, 40, 293-300.

Bainbridge used young rats divided into two groups, body weights and sex not given, as he found these not to be factors. To one group was given free access to the Halliburton-Drummond complete diet, to the other a similar diet except that the starch was replaced by butter of equal caloric value. Blood sugar tests and objective symptoms showed that the rats on the excess-fat diet developed a high resistance to insulin, much higher than the control group or that shown by rats upon ordinary laboratory diet. It is suggested that the explanation may possibly be hyperfunction of the thyroid on the excess-fat diet since it had previously been shown that excess-fat diet causes hyperplasia of the thyroid and that thyroidectomized rabbits are unusually sensitive to insulin. However, Bainbridge could not find, by weights or histological examination, any conclusive evidence of hyperplasia in the thyroids of the rats fed on the excess-fat diet. Bainbridge also found some evidence, but not conclusive, that excess-carbohydrate fat-free diet rendered rats more sensitive to insulin.—R. J. Seymour.

**A case of infantile diabetes treated with insulin.** Bowcock (H. M.) & Wood (J. A.), *J. Am. M. Ass. (Chicago)*, 1926, 86, 104-105; Abst., A. M. A.

Bowcock and Wood report their experience with eighteen months' treatment of an infant in whom diabetes was discovered at 16 months of age. Diet regulation and administration of insulin constituted the treatment. The striking feature in this case has been the practically normal increase in height, in contrast to the stunting of growth that was observed in diabetic children before the

advent of insulin. This case has been successfully managed without blood sugar determination, but the authors do not recommend the disregard of this helpful adjunct to the control of treatment. Blood sugar readings have seemed valueless in this case because of the apparent lability of the metabolic processes in this child. There was frequently observed in from two to three hours' time a change from a urine that was free of sugar and diacetic acid to a specimen loaded with both. Insulin reactions could be recognized only by objective symptoms, since the patient was unable to communicate his subjective feelings. Because of the difficulty in recognizing hypoglycemic reactions before they were well developed and because of the apparently very rapid change in blood sugar levels, the attempt to keep the urine constantly sugar free was abandoned. As the patient has grown older, this apparent lability of metabolism has decreased somewhat, and consequently it has been possible to decrease the insulin dosage slightly and give it in two daily injections instead of three. The decrease in insulin dosage while taking a quite constant and uniform diet suggests some improvement in tolerance.

Treatment of diabetes by raw fresh gland (pancreas). Carrasco-Formiguera (R.), Brit. M. J. (Lond.), 1925, 3378, 552-554.

The claim has recently been put forward that the ingestion of raw pancreas is highly beneficial in diabetes. This claim was tested by Carrasco-Formiguera on a boy of 7 who had not received insulin. The results were convincingly negative. The first day of subsequent insulin treatment diminished the urinary sugar to a trace.

—R. G. H.

The influence of the vagus on the islets of Langerhans. Part I.

Vagus hypoglycemia. Clark (G. A.), J. Physiol. (Lond.), 1924-1925, 59, 466.

It has been shown that the secretion of insulin is not necessarily dependent on the nerve supply to the islets; yet it is not unreasonable to suppose that the nervous system may influence their secretion, especially as there seems to be an antagonism between the sympathetic and parasympathetic systems. Possibly some mechanism of the parasympathetic system counteracts the hyperglycemia of sympathetic activity. Ergotamine does not cause a lowering of blood sugar, but when followed one hour later by pilocarpine or by guanidine, hypoglycemia results. That this is evidence of vagus influence is shown by the fact that after secretion of the vagus no hypoglycemia results from the injection of ergotamine followed by guanidine. It is concluded that stimulation of the vagus causes a secretion of insulin, which in turn causes hypoglycemia.—T. C. B.

An unusual case of hyperglycaemia (1.7%) with coma; associated with absence of acetone in the urine. Argy (W. P.), Boston M. & S. J., 1925, 193, 1236-1237.

A case is reported of coma in a colored male, aged 33, with typical symptoms of diabetes mellitus, existing over a period of six months and ending in death. It is marked by an absence of ketonuria, a high blood sugar concentration and a large amount of acetone in the spinal fluid. Nephritis was observed and this is suggested as a factor in the failure to excrete acetone. Active treatment with insulin, begun some hours after the onset of coma, reduced the blood sugar from 1714 mgm. per 100 cc. to 895 mgm. The patient, however, remained in a comatose state until death.

—J. C. D.

**Effect of insulin injection on the composition of milk.** Kamitani (E.), J. Pediat. (Tokyo), 1925, 921; Abst., Am. J. Dis. Child., 30, 719.

Kamitani experimented with two goats soon after they gave birth to kids. Insulin, distributed by the Cannaught Laboratories, was injected to the amount of 1 to 3 units per 2,000 kilograms of body weight and the milk was expressed at two hour intervals. The experiment demonstrated that the lactose in the milk showed a decrease of 17 per cent., and the duration of low carbohydrate was prolonged by increasing the dose of insulin. The acidity of the milk was also decreased at the same rate as lactose. The fat greatly increases in amount if the milk is expressed frequently, and the viscosity also increases proportionally. Giusti and Rietti once concluded that the milk fat is increased by insulin, but our experiment shows that the increase is not due to insulin. The effect of insulin on total nitrogen, calcium content, water and specific gravity is uncertain.

**Glucose infusions and insulin in the preparation of poor surgical risks.** Fisher (D.) & Mensing (E. H.), Boston M. & S. J., 1925, 193, 712-714.

The glucose is given intravenously very slowly. The injection should take not less than 90 minutes. One unit of U20 insulin is given for every 2 grams of glucose. Half of this amount is injected subcutaneously, when one-third of the glucose has been given, and the other half of the insulin when the glucose injection is completed. By following the urine and, if possible, the blood sugar closely accidents have been avoided. The authors found this method successful in 18 cases of shock and others have used it in acidosis of non-diabetic origin. The authors conclude that glucose infusions and insulin administered before operation in acute surgical conditions complicated by acidosis, shock, or incessant vomiting,

greatly diminish the operative risk and mortality, and transform a poor surgical risk into a fair or good risk. In general routine cases, particularly in gastric and gastro-intestinal conditions with or without inanition, glucose infusions and insulin have a remarkably invigorating effect, and greatly increase the operative percentage of safety. Glucose and insulin are indicated in those cases in which the patients are in good preoperative condition, but who are to undergo a serious operation, in which some difficulty is anticipated.—J. C. D.

**Trypsin and insulin injections into the pancreatico-duodenal artery.**  
Friedmann (T. E.) & Webb (P. K.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 69-72.

The observation concerning insulin is that when injected by this route in dogs it produces the characteristic fall in blood sugar. This is the opposite of what was found in cats by Epstein.—J. C. D.

**Significance of change in oxygen absorption after insulin in normal rabbits.** Hawley (Estelle E.) & Murlin (J. R.), J. Exper. Biol. & Med. (N. Y.), 1925, 23, 130-131.

The oxygen absorption as determined in respiration experiments rises the first hour after insulin injection and falls considerably below the pre-insulin level the second hour. The CO<sub>2</sub> elimination rises the first hour. The second hour it rises only slightly if at all and returns toward the pre-insulin level in the third and fourth hours. Study of the urinary nitrogen indicates an abrupt change in metabolism from fat to carbohydrate about 1½ hours after insulin. The diminished oxygen absorption for the second period is regarded as not due to the depression, but to the fact that additional oxygen is made available for combustion by bringing carbohydrate into metabolism in place of fat.—J. C. D.

**Spontaneous disappearance of diabetes.** John (H. J.), J. Am. M. Ass. (Chicago), 1925, 85, 1629-1631; Abst., A. M. A.

Two cases of diabetes associated with acromegaly with the data on a few other cases that have recently appeared in the literature have given the author a basis for serious consideration of the possibility of effecting a cure in certain cases of diabetes. In the two cases reported, a cure appears to have been established, as is indicated by the normal glucose tolerance curve secured in the first case, and in the presence of normal blood sugar values on a very heavy diet in the second. These cases add further evidence to the cases of apparent cure previously reported in the literature, and to the experimental work of Copp and Barclay in support of the belief that up to a certain stage the diabetic process is reversible.

The reduction of the death rate from diabetes, particularly from diabetic coma in Massachusetts. Joslin (E. P.), Boston M. & S. J., 1925, 193, 707-712.

The author first considers the statistics of deaths from diabetes and then gives brief instructions for the use of modern methods in treating diabetic coma. Deaths from diabetes per thousand of population have been on the increase since 1880. The rate of increase, however, has been getting less. The actual deaths in 1924 were fewer than for 9 years previous, omitting the war years, 1918-1919. The death rate from diabetes in Massachusetts per thousand is nearly twice that of London. In the first 3 decades the death rates are similar. In the fourth and fifth decades there are nearly twice as many deaths in London as in Massachusetts. This relation is reversed in the sixth decade when the diabetic deaths are higher in Massachusetts.—J. C. D.

Lactic acid and inorganic phosphorus of normals and diabetics after glucose, with and without insulin. Katayama (I.) & Killian (J. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 173-176.

In rabbits under urethane there was little change in the blood lactic acid after insulin. In normal human subjects at rest the lactic acid in the blood rose after the ingestion of 50 grams of glucose by mouth to 2 or 3 times its normal level. When insulin was given 2 to 3 hours following the glucose meal the lactic acid rose from 4 to 10 times its normal level. The lactic acid rose as the sugar fell. In diabetics glucose produced an increase of 50 to 100 times the normal amount of lactic acid. Insulin produced a rise, but not as marked as that in the normal subject. Insulin reduced the organic phosphorus in the blood and urine of both normal and diabetic subjects.—J. C. D.

The effect of insulin upon the metabolism of certain bacteria. Kendall (A. I.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 62-64.

Bacteria were grown in plain glucose broth and glucose broth containing insulin. The ability of the bacteria to utilize the glucose was then measured by the changes in the titratable acidity and hydrogen ion concentration. In the first group bacteria not normally utilizing glucose were tested, among them *Bacillus alcaligenes* and *Micrococcus catarrhalis*. The second group comprised *Bacillus bulgaricus* and *Bacillus acidophilus*, which, it has been reported, use more glucose in the presence of insulin. The third group was chosen from widely different groups and included several types of *pneumococci*, *streptococcus hemolyticus*, and *staphylococcus aureus*. In no case did insulin have any demonstrable influence on the organism's ability to use glucose.—J. C. D.

On the mechanisms of recovery of glycemia after the action of insulin (Sur les mecanismes de recuperation de la glycémie apres l'action de l'insuline). Lewis (J. T.) & Magenta (M.), Compt. rend. soc. de Biol. (Par.), 1925, 92, 821-822.

The mechanisms which cause recovery from the transient hypoglycemia caused by insulin are probably the same as those which cause hyperglycemia. Section of the splanchnics augments the sensitiveness to insulin. Hypoglycemia and convulsions follow a dose which only produces a moderate degree of hypoglycemia without convulsions in the controls. Section of the nerves of the hepatic pedicle augments slightly the sensitivity to insulin. Section of the two vagi diminishes the sensitivity a little. Simultaneous section of the splanchnics and vagi causes a disappearance of the marked sensitivity to insulin, but it is still somewhat greater than usual. Extirpation of the suprarenals in two operations, increase markedly the sensitivity to insulin. Suppression of the secretion of adrenalin either by extirpation of the medulla, or by removal of one suprarenal and denervation of the other, augments the sensitivity, but not as much as section of the splanchnics.—T. C. B.

Attempt at a surgical treatment of diabetes. Mansfield (G.), Klin. Wehnschr., 1924, 3, 2378-2380; Abst., Chem. Absts., 19, 3306.

The original idea was to sever the pancreatic duct, thus blocking the external secretion of the pancreas which might intensify the internal secretion. This was not tried because of the probable deleterious effect on food digestion of eliminating the pancreatic enzyme. A ligature was passed beneath the pancreatic vein and artery in the head of the pancreas and the pancreas tied off, exclusive of the blood supply, at this point. In this way only a portion of the external secretion of the pancreas was blocked. Dogs that had been so treated were persistently hypoglycemic after the effects of the surgical shock had subsided; they also showed an enormously high sugar tolerance which indicates that the internal secretion of the pancreas is increased when the external secretion is blocked.

Analogous action of insulin and epinephrin on the liver. Müller (E. F.) & Petersen (W. F.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 47-51.

The administration of .05 mg. of epinephrin per kilo of body weight raises the blood sugar of an animal (dog?) 50 per cent in two hours. Administration of 0.5 units of insulin similarly lowers it the same amount. If these doses are injected subcutaneously at the same time either separately or mixed, there is a decrease in blood sugar. In more than 60% of the cases this is greater than insulin alone would give. If the epinephrin is given 20 minutes before the insulin, the results are similar. These observations do not agree with those of MacLeod. He found that if the proper

amount of epinephrin was injected one hour after an insulin injection, there would be a counter balancing action between the two with a stabilizing of the blood sugar level. MacLeod considered that his experiments showed an antagonistic action between insulin and epinephrin. The authors take a different view. Insulin has two actions. The first is through the nervous system from the tissue depot where it is injected and results in the synthesis of glycogen by the liver. The second is the hormone action on the tissues resulting in their increased utilization of glycogen with the corresponding decrease in the amount in the blood. The authors explain the apparent conflict between their results and those of MacLeod as follows: Epinephrin given before or simultaneously with insulin delays the absorption of insulin; the nerve effect of the insulin depot initiates glycogenesis in the liver, and decrease in blood sugar follows. Epinephrin given an hour after insulin injection (when insulin has been completely absorbed and has reached its maximum effectiveness) mobilizes glucose from the liver, and thereby increases the already existing glucose mobilization. The glycogen store of the liver may thereby be practically exhausted, but the blood sugar level is maintained by the sufficiently rapid mobilization of glucose from the liver.—J. C. D.

**The use of high carbohydrate diets in the treatment of diabetes mellitus.** Sansum (W. D.), Blatherwick (N. R.) & Bowden (Ruth), J. Am. M. Ass. (Balt.), 1926, 86, 178-181.

With the use of high carbohydrate diets (2 or more gm. carbohydrate per gm. fat) it has been found possible to keep patients sugar-free and with a normal blood sugar. The patients are restored to a more nearly normal state of physical and mental activity. They are freed from the slightest traces of the acetone type of acidosis. The use of potatoes, milk and fruits has permitted the elimination of the acid-ash type of acidosis, which is believed to have been a cause of the high incidence of blood vessel disease. The diets are palatable. The patients lose their craving for forbidden foods, especially for the carbohydrates. A somewhat lower caloric intake is apparently required for full maintenance. These diets are cheaper, because they contain no special foods and much less of the expensive fats, such as cream, butter and olive oil. Theoretically, at least, and because of the entire freedom from acidosis, such diets should afford the patients the best opportunity for partial recovery.—R. G. H.

**A study of the mechanism of insulin. Part I. The action of insulin and of the salts of guanidine on the permeability of the mammalian erythrocyte.** Secker (J.), J. Physiol. (London), 1925, 40, 287-292.

From the brief review of the literature given, Secker feels

justified in concluding that whatever the fate of glucose under insulin that immediate and complete oxidation in the tissues does not occur. The suggestion of Haldane, Kay and Smith that insulin may cause changes in the permeability of the body cells led Secker to attempt laboratory tests of the hypothesis, using erythrocytes for the tests. Oxalated blood was used, this being divided into five parts for control purposes. The crucial tests were made upon two samples, one of whole blood to which small amounts (varying) of glucose were added, and the second to which both glucose and insulin were added. Because of the difficulty of obtaining properly washed corpuscles Secker thought it sufficient to estimate the amount of glucose in the whole blood and compare this with the amount found in the plasma after centrifugation, both containing equal added amounts of glucose and insulin. Results in every case showed that the glucose content of the plasma fell upon the addition of insulin while there was no effect upon the glucose content of the whole blood. This Secker believes must be explained by a change in permeability of the erythrocytes permitting substances in relative excess in either corpuscles or plasma to pass through the cell membranes. Checks by determination of chloride content and also by microscopic observation of the corpuscles in hypotonic and hypertonic salt solutions gave results that could be interpreted in the same way. Guanidine, in the presence of calcium, gave similar results to insulin. Secker suggests that since excision of the parathyroids causes an increase in the guanidines and a decrease in the calcium present that this may be a method by which the parathyroids influence carbohydrate metabolism.—R. J. Seymour.

**Influence of nutritive condition on initial fall in blood sugar after insulin.** Tiitso (M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 40-43.

Rabbits were starved for one and two weeks and their reaction to insulin tested against that of normal well fed animals. In an hour after injection the blood sugar had been reduced 74.5 mg. per cent in the controls, while it had fallen only 54 mg. in animals starved one week and 48 mg. per cent in those starved two weeks. Starved animals are, therefore, more resistant to the action of insulin than well fed ones.—J. C. D.

**Influence of high temperature on insulin (Sulla influenza esercitata dalle alte temperature sulla conservazione dell' insulin).** Trocello (E.) & Cruto (A.), Rassegna di clin. terap. (Roma), 1924, 23, 229-233.

Insulin in a solid state has a greater resistance to heat than insulin in solution. Solid insulin is not destroyed by a temperature of 100° C. for 24 hours, nor of 42° C. for 30 days. The solution has

kept its initial activity at 100° C. for 10 hours, while it is reduced  $\frac{1}{2}$  in 24 hours at 100° C., or 16-34 days at 36° C. Such a study is important in relation to the preservation of insulin in tropical regions.—P. M. N.

**Heteroplasia of endocrine glands in diseases of the nervous system**  
(Die Heteroplastik der endokrinen Drüsen bei Erkrankungen des Nerven-systems). Brodsky (J.), J. f. Psychol. u. Neurol. (Leipz.), 1923-1924, **30**, 77-86; Abst., Physiol. Absts., **10**, 423.

Description of two cases of tetany which were to all appearances completely cured by the intramuscular grafting of the fresh parathyroid glands of a goat. This animal was chosen because the catalase index of its blood (determined by Bach and Zubkowa's method) was the nearest possible to that of the blood of the patients.

**The action of Collip's parathyroid extract on blood and cerebro-spinal fluid calcium.** Cameron (A. T.) & Moorhouse (V. H. K.), Trans. Roy. Soc. Can. (Montreal), 1925, **19**, 39-43; Chem. Abst., **19**, 3524.

Collip's results with parathyroidectomized and normal dogs, and with his standardized extract are confirmed. In the parathyroidectomized animal serum, plasma and cerebrospinal fluid calcium tend to be restored to normal values, and in the normal animal repeated injection raises all three, the ratio remaining constant.

**Internal secretions of the parathyroid glands.** Collip (J. B.), Proc. Nat. Acad. Sc. (Balt.), 1925, **11**, 484-485; Abst., Chem. Absts., **19**, 3530.

The general principles involved in the preparation of the product are dissolution of the gland by controlled acid hydrolysis and isoelectric fractionation of the active principle. The hormone so obtained is specific for parathyroid tetany in dogs. The physiological effects of the active principle are related mainly to the calcium metabolism. The degree of increase of calcium in the blood is directly related to the amount of the principle which permits a determination of the potency of the extracts.

**Further studies on the physiological action of a parathyroid hormone.** Collip (J. B.) & Clark (E. P.), J. Biol. Chem. (Balt.), 1925, **64**, 485-507.

Stronger extracts than previously reported (J. Biol. Chem., 1925, **63**, 395) are prepared by the use of methods used for protein purification. The authors find that repeated small doses of this extract produces a cumulative action which ultimately results in

death, while a single large dose causes a transitory hypercalcemia from which the animal always recovers. In the former the intravenous injection of 25% glucose or 15% sodium chloride delays the fatal termination, but there is no complete antidote. The authors offer as a provisional unit the 1/100 of the amount of extract which will produce an average increase of 5 mgms. in the serum calcium of normal dogs weighing 20 kg. over a period of 15 hours. They emphasize the necessity of using a number of animals to eliminate individual differences. Studies of dogs carried to fatal termination show that the N.P.N. increases prior to death, which the authors regard as a terminal phenomenon. Hypercalcemia is produced, which they attribute to the specific hormone action, and total nitrogen and chlorides diminish which they ascribe to the loss of blood. With the establishment of hypercalcemia the blood phosphorous values increase. The degree of hypercalcemia produced by parathyroid injection is greater in normal than in thyroparathyroidectomized animals, but the differences are slight. Blood volume apparently diminishes. The authors were unable to observe any unequivocal influence on blood pressure. Simultaneous administration of potent parathyroid extract and guanidine to normal dogs at regular intervals has resulted in a condition of tetany and of profound hypercalcemia. Death has resulted in such experiments within approximately the same time as in the case of animals receiving parathyroid extract only. The article is illustrated with numerous informative charts.—A. W. R.

**Comparable cell changes in central nervous system in cretinism, parathyroid tetany and fatigue.** Dye (J. A.), J. Exper. Biol. & Med. (N. Y.), 1925, 23, 119-121.

The central nervous systems of five cretin lambs and two cretin goats were compared with those of normal animals. Sections were taken from the motor cortex, thalamus, mid brain, cerebellum, medulla oblongata and cervical enlargement of the spinal cord. These were stained by a modification of Nissl's method. Chromatolysis distinct though variable was present in the thyroidless animals. Similar sections from 13 dogs with experimental tetany and from sixteen white rats that had been exercised by swimming showed changes similar in nature though varying in degree.

—J. C. D.

**Effects produced by extracts of parathyroid glands on normal and parathyroidectomized dogs.** Fisher (N. F.) & Larson (E.), Am. J. Physiol. (Balt.), 1925, 75, 93-106.

Relatively pure acid extracts of ox-parathyroids were prepared. These extracts were used with decided success for the relief of tetany in a series of eighteen thyro-parathyroidectomized dogs kept

on a meat diet to hasten and increase the severity of tetany. The extracts had a decided action not only in increasing the calcium of the blood serum but the inorganic phosphorus and non-protein nitrogen as well. Some of the animals, after control of the tetany during the first few weeks, did not show any signs of tetany thereafter in spite of a continued low calcium level—below 6 mgm. per 100 cc. of blood serum.—Author's abst.

**Parathyroid:** An extract obtained from the external bovine parathyroid glands capable of inducing hypercalcemia in normal and thyreoparathyroprivic dogs. Hjort (A. M.), Robison (S. C.) & Tendick (F. H.), J. Biol. Chem. (N. Y.), 1925, 65, 117-128.

Bovine parathyroid glands were extracted by water, 65% alcohol, acetic acid in alcohol, aqueous and alcoholic sodium hydroxide, ether, acetone, and aqueous and alcoholic hydrochloric acid. An extract which induced hypercalcemia in normal and thyreoparathyroprivic dogs was obtained only when the glands were digested with aqueous or alcoholic hydrochloric acid. It was found that a hormone is obtainable from fresh bovine parathyroid glands by aqueous or alcoholic hydrochloric acid extraction which, when given parenterally to dogs, possesses the property of relieving tetany and inducing hypercalcemia. Boiling the glands with dilute hydrochloric acid is preferable to extraction at room temperature. The lipoid-free portion of the glands is the potentially active tissue. Very little, if any, potency is lost in the removal of proteins by neutralization to the isoelectric point and addition of alcohol to a concentration of 80%. The hormone is relatively stable as judged by the vigorous treatment it withstands in the course of its preparation, and its retention of activity during 16 months preservation in the ice-chest. Definite conclusions are in some cases not justified because of the limited accuracy of the hypercalcemia test.—Authors' Abst.

**Histological studies of normal and pathological human parathyroid glands.** Kurokawa (K.), Japan Med. World (Tokyo), 1925, 5, 250-251.

A careful histological study was made of 815 parathyroid glands from 240 human subjects ranging in age from late fetal to 80 years. It was found that anatomically the parathyroids become larger with advance of age, but there is no physiological atrophy. Their development is most marked at the period of adolescence. During the fetal life the parenchyma cells are composed only of clear chief cells. These cells, however, begin to decrease at about the period of adolescence, and the dark cells begin to appear; in adult the dark chief cells predominate. The clear chief cells contain a large quantity of glycogen, but no fatty substance; the dark chief cells contain a large quantity of fatty substance instead of

glycogen. Consequently the quantity of glycogen or fatty substance is influenced by the number of each type of the chief cells. The oxyphile cells begin to appear at about the period of adolescence and there is a tendency to increase. These cells do not usually contain glycogen or fatty substance. If they do it is only in trace. The quantity and the time of appearance of follicles and colloidal formations are about the same as those of the oxyphile cells. The time of appearance and quantitative fluctuation of the dark chief cells and the oxyphile cells begin at the time when the development of parathyroid is most marked, which is the period of adolescence. The oxyphile cells are larger than the chief cells and rich in stainable substances. The protoplasma and nuclei do not show any degenerative changes. The appearance or increase of the oxyphile cells is not accompanied with increase of intercellular tissues, which may be regarded as atrophic changes. The oxyphile cells increase with advance of age, but the increase does not represent senile changes. The oxyphile cells appear in masses and often form nodules, some of which may be seen with the naked eye. The parathyroid gland shows no physiological atrophy. The oxyphile cells appear at the time when the clear chief cells begin to decrease with increase of the dark chief cells and they also increase during pregnancy. These facts indicate that they have some important function.

In status lymphaticus, there was found lipomatosis and atrophy of the parenchyma with marked increase of the oxyphile cells. In adult beri-beri, there is a marked increase of the clear chief cells. In infants the clear chief cells are hypertrophic. In chronic tuberculosis, the increase of intercellular connective tissue is very marked (cirrhosis). In syphilis the picture is about the same as in cirrhosis. In tumor cases, as a rule, the oxyphile cells are increased. In pregnancy, the oxyphile cells are also increased. In sarcoma of bones, there was found marked follicular formations.

—R. G. H.

Observations upon the effects produced in normal and parathyroidectomized dogs and herbivorous animals by injections of parathyroid extract. Macleod (J. J. R.) & Taylor (N. B.), Trans. Roy. Soc. Can. (Montreal), 1925, 19, 27-38; Abst., Chem. Absts., 19, 3524.

Collip's results with parathyroidectomized and normal dogs are confirmed. In normal dogs the temperature was raised after the first injection and remained high. Results suggest that fat, either in the diet, or in the fat reserves of the body, may be protective against the action of the extract. Herbivorous animals appear to be resistant to the action of the extract.

**Parathyroid extract in treatment of a case of tetany.** Snell (A. M.),

J. Am. M. Ass. (Chicago), 1925, 85, 1832-1833; Abst., A. M. A.

A case cited by the author illustrates the effect of Collip's parathyroid extract on the blood calcium level in a clinical case of chronic parathyroid tetany. The marked clinical improvement, the decrease of electrical excitability, and the disappearance of the signs and symptoms of tetany attest the therapeutic value of the substance. The rather large dosage required may possibly be attributed to the relatively low potency of the preparation used. The method of "pyramiding" was used. From 1 to 2 c.c. of the extract was given subcutaneously every two hours, a total of from 5 to 10 c.c. each day. A daily rise in blood calcium was noted, and the average level tended to rise, without, however, reaching normal levels. The diet was maintained at a constant level throughout. All other treatment had been discontinued. Subjective improvement was marked; the patient's restlessness and excitability decreased, and Chvostek's sign was elicited only with difficulty. On the resumption of calcium lactate by mouth, the injection of the extract was discontinued; under this method of management, the serum calcium was relatively constant and the patient appeared to feel fairly well. From 10 to 15 gm. of calcium lactate and 10 c.c. of the parathyroid extract were then given daily. The conjoint use of the two drugs resulted in a rise of the blood calcium to normal, with complete disappearance of every sign and symptom of tetany. Calcium lactate administered alone in maximal dose did not produce and maintain a normal level of blood calcium. The same is true of the dosage indicated for parathyroid extract alone. The combined treatment of calcium and parathyroid easily sufficed to attain and maintain a normal blood calcium level and coincidentally to cause the disappearance of all the signs and symptoms of tetany. The patient feels normal for the first time since the onset of her illness.

**The effect of ultra-violet radiation upon experimental tetany.**

Swingle (W. W.) & Rhinhold (J. G.), Am. J. Physiol. (Balt.), 1925, 75, 59-69.

Experiments were made on ten dogs using a mercury vapor lamp 30% of the spectral energy of which was in the form of ultra-violet rays. The distance was 40 cm. or less. It was found that exposure of normal dogs to ultra-violet rays for one hour a day for periods ranging from four to twelve days does not appreciably alter the level of the serum calcium. It may even be slightly diminished in some animal. Radiated dogs develop tetany following parathyroid removal as rapidly as normal non-radiated dogs fed the same diet. Radiation of parathyroidectomized dogs greatly prolongs the life of such animals and brings about a striking amelioration of the violent symptoms. Radiated animals may live for twenty-five days

after the first appearance of tetany symptoms, but sooner or later die of tetany or exhaustion. The calcium content of the blood serum of such operated dogs is low and prolonged radiation does not raise it to normal. The amelioration of tetany symptoms by ultra-violet rays and prolongation of life of parathyroidectomized dogs is probably due to the effect of such radiation in increasing the absorption and retention of the small amounts of calcium obtained from the food, so that its elimination from the blood and tissues is less rapid than in non-radiated parathyroidectomized dogs.

—R. G. H.

**The effects of parathyroid feeding on calcium and creatine metabolism.** Woodman (D.), Bio-Chem. J., (Liverp.), 1925, 19, 595-600.

Young and adult rats were used for the study. The experimental procedure consisted in the administration either of desiccated parathyroid by mouth or parathyroid extract by injection. The influence of calcium lactate both with and without parathyroid medication was also studied. Muscle creatine, urine creatine and creatinine and bone calcium were all determined by generally accepted standard methods. The author concludes that parathyroid medication has no effect on body weight or on bone calcium. Appetite is increased. No change is observed in muscle creatine which the author explains by the assumption that the muscles are already saturated. The creatine content of the urine increases while the creatinine fraction diminishes under the stimulus of parathyroid feeding. This would seem to indicate that muscle creatine is the precursor of urinary creatinine as Hammett (Am. J. Physiol., 1921, 56, 196) has shown that the conversion of creatine into creatinine in incubated muscle is inhibited by parathyroid extract.—A. W. R.

**The action of parathyroid extracts on guanidine.** White (F. D.) & Cameron (A. T.), Trans. Roy. Soc. Can. (Montreal), 1925, 19, 45-52; Abst., Chem. Abst., 19, 3524.

Vine's method for estimation of activity of parathyroid preparations shows negligible activity when used with Collip's active extract. The inhibiting influence of complex substances such as arginine or nucleic acid derivatives on the precipitation of guanidine picrate appears to be responsible for the results obtained by Vine's with animal tissues, so that such results probably bear no relation to the functions of these tissues. Marsten's reagent for guanidine estimation reacts with nitro-guanidine and galegine, and slightly with arginine, giving the 2 latter a rose-red color. Parathyroid extracts have little or no effect on guanidine, judged by this test, which excludes change into creatine, creatinine, or methyl-guanidine. Guanidine picrate is much less soluble in picric acid than in water.

The pineal of birds (*La pineale negli ucelli normali e cerebro-lesionati*). Desogus (V.), *Riv. di biol. gen.* (Torino), 1924, 6, 495-504; *Abst., Physiol. Absts.*, 10, 422.

During sexual activity the glandular cells of the pineal body of birds become larger, and shows signs of secretory activity. The phenomenon is observed in both sexes, but particularly in females. After a cerebral lesion performed during a phase of maximal sexual activity both the germ organs and the pineal body fall into a state of noticeable hypofunction.

Concerning the origin of concretions and pigment in the pineal gland (*Über die Entstehung von Sandkörnern und Pigment in der Zirbeldrüse*). Lignac (G. O. E.), *Beit. z. path. Anat. u. z. allg. Path.* (Jena), 1924-1925, 73, 366.

The author has made a macro- and micro-scopic study of pineal concretions and discusses their origin from the standpoint of Liesegang's "rhythmic" precipitation of colloids. He likewise discusses the derivation and nature of the pigment bodies. He characterizes the former as spheroliths of concentric structure produced by the simultaneous precipitation of permanent irreversible colloids and of crystalloids. The former function as protective colloids in the gland cell. While nothing is known of their nature, he suggests that they may belong to the myelin group. Two pigmentary bodies are identified. One a yellow substance found in pineal and glia cells and increases in concentration with age. The second is a brownish substance which seems to possess a certain similarity to the skin pigment and is derived from the nuclei of the cells. Those portions staining with pyronin are regarded as a possible source. Several illustrative plates and a brief bibliography accompany the article.—A. W. R.

The influence of the suprarenal gland on the thymus. III. Stimulation of the growth of the thymus gland following double suprarenalectomy in young rats. Jaffe (H. L.), *J. Exper. M.* (Balt.), 1924, 40, 753.

In view of the fact that previous observations showed that double suprarenalectomy in the rat, if carried out after involution had normally begun, brought about regeneration of the thymus gland, it was decided to study the effect of suprarenalectomy on young rats before puberty or before involution of the thymus had set in. The material included a study of 39 young rats, varying in age at operation between 35 and 54 days. Twenty-five of these rats were suprarenalectomized. Of these 25, 11 died from 1 to 41 days after the extirpation and were excluded from the experiments proper. The remaining 14 were sacrificed at two weeks' intervals from 2 to 8 weeks after operation and the weights of their thy-

muses compared with those of 14 control rats. Eleven of the control rats were litter mates of the animals operated upon. The thymus gland of each of the 14 suprarenalectomized rats was heavier than that of its respective control, the difference varying from 12% to 85%. The average thymic weight of the 14 suprarenalectomized rats was 49% greater than that of the controls. This thymic hyperplasia was apparent soon after suprarenaectomy, the maximum effect being attained usually within two weeks. Prepubertal thymic hyperplasia following suprarenaectomy may offer a partial explanation of the pathogenesis of status lymphaticus. In the human cases, hypoplasia of the suprarenals is one of the outstanding pathological findings together with a large thymus and prominent lymph nodes. While earlier authors emphasize the hypoplastic changes of the chromaffin tissue, the later work of Marine and Baumann on the rabbit and our work on the rat clearly indicate that the lymphoid overgrowth is dependent upon interrenal and gonadal insufficiency.—Author's Abst.

**Experimental studies on the formation of Hassall's corpuscles.**

Jaffe (H. L.) & Plavská (Alexandra), J. Exper. Biol. & Med. (N. Y.), 1925, 23, 91-93.

Autoplastical transplants of the thymus were made in guinea pigs 30 to 45 days old. The microscopic changes in the transplants were followed for 48 days. The authors conclude that these studies seem to bring unequivocal experimental proof that Hassall's corpuscles are derivatives of the reticular epithelium, a view originally proposed by Paulitsky and more recently elaborated by Hammar, and supported by many others on the basis of embryological and post fetal histological studies. They also show that in post fetal life the formation of Hassall's corpuscles is independent of the presence of remnants of the original epithelial ducts of Remak.—J. C. D.

**Influences of the constituents of thymus gland cells on the growth of young organism.** Miyagawa (Y.) & Wada (K.), Japan Med. World (Tokyo), 1925, 5, 275-289.

Aqueous extract of calves' thymus gland was injected into a considerable number of young white rats and a few young dogs. The work was controlled by similar injections of kidney or lymph node extracts. With optimal doses of thymus extract (0.05 gm. thymus per kg. body weight) a marked accentuation of growth was observed, with larger doses (1.0-2.0 gm.) growth was retarded, presumably on account of toxic effects. In a few instances extracts of thyroid gland were found to depress growth.—R. G. H.

**Skeletal changes in human fetuses as a result of undernourishment of the mother during pregnancy (Die Änderungen im Knochen-**

**system der Früchte während der Schwangerschaft bei Unterernährung.** Stefko (W.), Ztschr. f. Konstit. (Berl.), 1925, 10, 742-754.

In examining human fetuses from 4 to 7 months and newborn in which the mother had been undernourished to various degrees, the obvious endocrine change in the offspring was an unusually early involution of the thymus.—A. T. R.

**Observations on effects of iodine administration in dogs following hemithyroidectomy and unipolar ligation.** Barber (W. H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 167-169.

There was much less hyperplasia of the thyroid cells in this series than in a previous series of dogs similarly operated upon in which iodine was not given.—J. C. D.

**Adenomatosis, or the diffuse adenomatous goiter.** Else (J. E.), J. Am. M. Ass. (Chicago), 1925, 85, 1878-1882; Abst., A. M. A.

Else asserts that adenomatosis of the thyroid is a definite pathologic entity differing from adenoma in that the process is diffuse and does not have a true capsule. Adenomatosis produces a hyperthyroidism of the cardio-vascular type. It is important to differentiate between adenoma and adenomatosis because the former requires simple enucleation of the tumor growth, while the latter requires subtotal double lobectomy.

**Autolysis of the thyroid gland.** Ferrero (V.), Arch. d. sc. med. (Par.), 1925, 47, 294-301; Abst., Chem. Absts., 20, 58.

In small pieces of the canine thyroid subjected to aseptic autolysis there occurs from the fourth to the sixteenth hour a gradual destruction and final complete dissolution of the alveolar colloid, preceding the alterations occurring in the thyroid tissue itself. This is believed to indicate the presence in the gland of an enzyme capable of rendering the colloid soluble and hence capable of absorption during life.

**Osseous and muscular changes in thyroidectomized sheep.** Goldberg (S. A.) & Simpson (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 132-133.

In cretin sheep and goats the abdomen and digestive tract were flabby and distended. The femurs were atypical with an increase in red marrow, a persistence of epiphyseal cartilages and other changes. The skeletal and cardiac muscle showed changes, particularly a practically complete absence of cross striations. These changes seem to indicate that as a result of the thyroidectomy there are degenerative changes following an arrested development of the osseous and muscular tissues.—J. C. D.

**Hypothyroidism.** Grigsby (C. M.), South. M. J. (Birmingham), 1926, 10, 4-5.

The author discusses larval myxedema, as contrasted with cretinism and marked progressive myxedema. He gives the symptoms emphasizing the reduced metabolic rate as an important one and then outlines the treatment. He uses thyroid extract starting with small doses and gives thyroxin only in obstinate cases.

—J. C. D.

**The changes in the blood sugar which follow experimental thyroid feeding.** Hancher (K. G.), Hupper (Marjorie), Blau (N. F.) & Rogers (J.), Am. J. Physiol. (Balt.), 1925, 75, 1-5

The oral administration to 32 dogs of a glycerol extract of hashed fresh (pig) thyroid glands produced a marked and sustained rise in the sugar content of the animal's blood. This was not shown by any of four commonly used commercial preparations of the medicament. One of these, in fact, caused an immediate and distinct decrease in the blood sugar.—R. G. H.

**Iodin hyperthyroidism—an analysis of 50 cases.** Jackson (A. S.), Boston M. & S. J., 1925, 103, 1138.

The appreciation of the value of iodine in the treatment of goitre has resulted in its indiscriminate and unwise use both by physicians and the public, so that the incidence of iodine hyperthyroidism is increasing. In 40 of the 50 cases iodine had been prescribed by a medical man. In iodine hyperthyroidism the pulse does not have the low diastolic pressure found in exophthalmic goitre. The basal metabolic rate in this series averaged 31% plus, in a group of toxic adenoma, 29%, and in a series of exophthalmic goitre cases, 54% plus. The disorder of the gland resembles toxic goitre. Three patients in this series died. Eleven were treated medically and the rest by operation. Of the forty for which there are proper records all showed a marked reduction in metabolic rate and a gain in weight.—J. C. D.

**Induced hyperthyroidism.** Kimball (O. P.), J. Am. M. Ass. (Chicago), 1925, 85, 1709-1710; Abst., A. M. A.

In order to determine if possible whether or not harm may result from the routine use of iodin in the prophylaxis of goiter as it has been carried out in the Cleveland district since 1917, a study has been made by Kimball of those cases of hyperthyroidism in which some form of iodin has been administered. In 309 cases it appeared that the symptoms of hyperthyroidism had been precipitated or made worse by the use of iodin. In 210 cases the goiters were of long standing, the average period being eighteen years. In each of these cases, the gland was clinically or microscopically

adenomatous. In this group of 309 cases, there were six cases in which the only source of iodin had been iodized salt. All of these patients were women past 40 years of age, and each had a nodular goiter of long standing. Thirty-seven patients had taken iodin of their own volition; several had taken a solution of sodium iodid, but the great majority had used repeated external applications of tincture of iodin over the goiter. The most striking fact brought out by this study is that five-sixths of the patients having induced hyperthyroidism had been taking iodin as prescribed by their physicians. In twenty-one cases of goiters of long standing, compound solution of iodin (Lugol's solution) had been given for weeks, in doses of from 5 to 10 drops, three times a day. In many cases, 5 drops of the solution of sodium iodid, three times a day, had been prescribed, and a considerable number of these patients had taken this medication for as long as three or four months. One boy, aged 16 years, who had a congenital adenoma, had taken syrup of ferrous iodid, 1 dram (3.75 c.c.), three times daily, continuously for eighteen months. In 84 per cent of the cases of toxic goiter the physicians had prescribed large doses of iodin to be taken over a long period of time, and this treatment had been given in spite of the fact that the goiter was of long standing and in many cases, nodular in type. Kimball says that, in all cases of iodin treatment, the dosage should be considered in terms of milligrams. The maximum dosage for an adult, provided there are no contraindications, is 10 mg. daily for not longer than one month, during which time the patient should be under very close observation. Long standing goiters in adults should be treated surgically, if any symptoms of hyperthyroidism are present. In young adults and in adolescents, medical treatment should first be tried. There is apparently no danger in the routine prophylaxis of goiter as it is carried out through the schools; namely, the administration of 10 mg. of iodin weekly. Among forty cases of exophthalmic goiter in children, only one child had been given iodin. In this case the patient had received the prophylactic treatment of 10 mg. of iodin a week for one month, three months before the onset of the acute hyperthyroidism, and a review of the history shows that the onset of the hyperthyroidism in this case was a coincidence and not a result of the month of iodin treatment. In the medical treatment of goiter in adults, Kimball emphasizes the importance of care in the selection of cases; the use of small amounts of iodin for not longer than one month, and the necessity of close observation throughout this period.

**Studies in endocrinology. Hypothyroidism with and without myxedema.** Lawrence (C. H.), Boston M. & S. J., 1924, 190, 8-21.

This article is based on a clinical and laboratory study of twenty-five cases of hypothyroidism, all adults. There were twenty-

one females and four males, the usual ratio in thyroid failure. In only four cases was there a family history of endocrine disease. In fourteen cases the onset of the failure was referred by the patients to an acute infection or strain. In the remainder there was no definite etiology obtained in the history. The average duration of the condition was over eight years, showing how frequently hypothyroidism escapes detection. The author reports fully on a case of thyroid failure without myxedema, giving the physical and laboratory findings, before and after treatment, and emphasizes the existence of a non-myxedematous type of hypothyroidism which is often not recognized by the clinician. Eight of the patients in his series were of this type. The various findings in all the cases are tabulated. Attention is called to the high blood nitrogen in the majority of cases and the question is raised concerning the possible relation of abnormal nitrogen metabolism to the early arteriosclerosis of hypothyroidism. The author emphasizes the more simple tests which should at least raise the suspicion of thyroid failure in the absence of myxedema.—Author's Abst.

**Exophthalmic goiter question.** Liek (E.), *Deutsch. Ztschr. f. Chir.* (Leipz.), 1925, 193, 246; Abst., *J. Am. M. Ass.*, 85, 1845.

The author emphasizes the significance of the brain in the pathogenesis of exophthalmic goiter. He has scarcely ever encountered a case without a history of some grave psychic trauma. Psychoanalysis may help in treatment, in the beginning as well as before and after surgical treatment. He prefers the latter to roentgen therapy except in adolescents. The operation should be made in a favorable phase of the disease. The mental condition of the patient is prognostically more important than the basal metabolism. The intervention should be extensive, but without attempt to get the thymus. He deplores the frequent overlooking of the psychic condition by self-styled "sober thinking" surgeons and attributes it to the loss of mental versatility occurring in every mechanism of mental work. This leads to a sort of self-righteous mandarin attitude, and wrong judgment as to success and failure.

**Blood flow and blood pressure in exophthalmic goiter.** Liljestrand (G.) & Stenstrom (N.), *Acta Med. Scand. (Stockholm)*, 1925, 43, 99-129.

The minute volume of the heart during rest was determined in 7 females and 3 male healthy subjects and in 8 females and 3 males suffering from exophthalmic goiter. A considerable increase in the minute volume was found in the diseased subjects, amounting on an average in the female patients to 80%, in the male to 100%. The utilization of the oxygen of the blood was somewhat lower than normal, so that in addition to the increased metabolism

other factors may also have been responsible for the augmented blood flow. The systolic blood pressure in the patients was somewhat increased, the diastolic pressure showed a slight decrease. The considerable increase in the work of the heart which is a consequence of the increase in minute volume and mean blood pressure, seems to play an important part in the development of those symptoms from overstrain of the heart which often occur in exophthalmic goiter.—Author's Summary.

**Development of the pineal gland in infancy (Die Entwicklung der Zirbeldrüse in Säuglingsalter).** v. Meduna (L.), *Ztschr. f. Anat. u. Entwicklungs gesch.* (Berl.), 1925, **76**, 534-547.

Meduna concludes that on the whole the development of the pineal gland indicates that it is an endocrine organ. The parenchymal cells, while regarded as *sui generis*, are related to the glia cells, having a common ectodermal origin.—A. T. R.

**The interaction of thyroid and adrenals as shown by the respiratory metabolism (Das Zusammenwirken von Schilddrüse und Nebenniere, geprüft am respiratorischen Stoffwechsel).** Nakayama (K.), *Biochem. Ztschr.* (Berl.), 1925, **155**, 386-412.

The author has studied the respiratory metabolism of rats by the differential method with controls (Asher-Takahashi, *Biochem. Ztschr.*, 1924, **145**, 130). The adrenal influence is studied by suprarenin injections, using both the subcutaneous and intramuscular routes. Normal rats under these circumstances exhibit great increases in the oxygen consumption and carbon dioxide elimination. Thyroidectomy inhibits this action very markedly, although the injections produce the same qualitative result. The simultaneous use in normal rats of suprarenin injections and thyroid extract by mouth produces very great increases in the metabolic level which is repeated although in lesser degree when previously thyroidectomized rats are used. By a careful study of the time element the author feels that he has demonstrated that a slower rate of absorption is not the inhibiting factor in the experimental animals. He concludes that the thyroid hormone is a potent activator of the parasympathetic and sympathetic nervous systems. This conclusion is not modified by the fact that the activation of adrenalin by the thyroid is not rigorously specific. The article contains very complete protocols of the experimental results.

—A. W. R.

**The effect of extirpation of thyroid and spleen on the basic respiratory metabolism as influenced by injections of suprarenin (Über**

die Wirkung von Schilddrüsen und Milzextirpation auf den durch Adrenalininjektion beeinflussten respiratorischen Grundumsatz.). Nakayama (K.), Biochem. Ztschr. (Berl.), 1925, 155, 436-458.

The third paper in the series (Biochem. Ztschr., 1925, 155, 387 and 413) using similar methods. The author finds that the removal of the spleen after thyroidectomy still further lessens the stimulating action of suprarenin injections initially produced by thyroidectomy alone. The complete removal of the spleen from otherwise normal animals may inhibit the response of the organism to suprarenin, but does not necessarily produce this result. The simultaneous removal of both thyroid and spleen produces divergent and contradictory results, in some instances increasing, in others decreasing the effect on the gaseous metabolism of suprarenin injections. If the spleen be first removed and later there be extirpation of the thyroid, the subsequent use of suprarenin, subcutaneously administered, may cause a notable increase in the gaseous metabolism. Full protocols are included.—A. W. R.

#### Present-day surgical treatment of diseases of the thyroid gland.

Pemberton (J. D.), J. Am. M. Ass. (Chicago), 1925, 85, 1882-1886; Abst., A. M. A.

In the Mayo Clinic, in 1924, there were 1,928 operations on 1,725 patients with goiter. Ten patients died, a mortality by operation of 0.51 per cent and by case of 0.58 per cent. There were 677 patients with goiter unassociated with hyperthyroidism, with no deaths; 368 patients with hyperfunctioning adenomatous goiter, with four deaths (1.08 per cent), and 741 patients with exophthalmic goiter, with six deaths (0.8 per cent). This extremely low mortality rate achieved by present-day surgical treatment of the thyroid gland, according to the author, was made possible by the perfection of operative technic and the discovery of means of controlling hyperthyroid crises. The employment of the multiple-stage operation in selected cases, and refinements in management designed for the protection of the patient resulted in a tremendous reduction in the operative mortality and served to establish firmly the surgical treatment of exophthalmic goiter. However, on account of the failure to eliminate the hyperthyroid crises completely, and because of the obvious objections to the multiple stage operation, this method left much to be desired. The proper administration of iodin to patients with exophthalmic goiter has completely controlled both the spontaneous and the postoperative hyperthyroid crises. The influence of iodin on the surgical treatment of exophthalmic goiter

is shown by the following clearly proved facts: 1. The convalescent period has been definitely shortened. 2. The necessity for multiple operations has been greatly decreased. 3. The limits of operability have been widened. 4. The mortality has been further reduced. The problem presented by the patient with hyperfunctioning adenomatous goiter is one of procrastination, and the hope of its solution lies in the education of the public to the fact that all nodular goiters are potentially dangerous and should be removed unless the patient is kept under periodic medical observation.

**Iodids in substernal goiter in childhood.** Petemyi (G.), Monatschr. f. Kinderh. (Leipz.), 1925, 30, 419; Abst., Am. J. Dis. Child., 30, 881.

In two cases in which substernal goiters produced such pressure symptoms as to suggest the necessity of operation, potassium iodid in doses of 25 mg. twice a day relieved all the symptoms.

**The histological changes brought about in cases of exophthalmic goiter by the administration of iodine.** Reinhoff (W. F., Jr.), Johns Hopkins Hosp. Bull. (Balt.), 1925, 37, 285-306.

Brief historical sketch pointing out the close relationship of iodine to endemic goiter as well as the physiological hypertrophies in man and animals. Three clinically typical cases of exophthalmic goiter are reported. In each of these the basal metabolic rate was well above fifty. (Since this report five more cases have been so studied with similar results.) Iodine had not been administered in any form. Under local anaesthesia one entire right upper pole of thyroid gland was removed. It was fixed in Zenker-formalin and embedded in paraffin. Serial sections revealed the characteristic microscopical picture of exophthalmic goiter. The patients then received Lugol's solution, 10 minims, 4 times daily for 2-3 weeks. In all cases the patients improved markedly, the pulse and basal metabolic rate becoming normal. Double partial lobectomy was then performed and the gland compared in gross and microscopic features with the portion removed at first operation. The following changes had occurred. The gland increased in size, became more hard or rubber like in consistency and nodular in contour. Thrill and bruit at the poles had disappeared. Vascularity decreased with marked increase in amount and density of colloid. Scarring as well as the fibrous stroma of the gland was augmented. Involutional sequelae in the form of large colloid cysts, localized and encapsulated, dilated colloid acini resembling so-called colloid

adenomata were seen. The bulging, active epithelial cells which before iodine was given contained large vesicular nucleus and colloid-like droplets after iodine were shrunken, containing no colloid droplets and pyknotic nuclei. The blood vessels were collapsed and some thrombosed. The acini which were papillomatous and lace-like before iodine were more regular in contour and distended to maximum capacity with colloid. Fifteen other cases studied gave similar findings. The series shows that iodine produces an artificial clinical remission in cases of exophthalmic goiter, which is accompanied by a change in the histological picture from hyperplastic to a colloid state. The colloid state, therefore, clinically, as well as histologically, is less active than the hyperplastic state. A clinical remission, artificial or natural, in a case of exophthalmic goiter, is associated with a change in the histological picture from a hyperplastic to a colloid state. There may be enough hypertrophy and hyperplasia remaining after the clinical remission to characterize the tissue histologically as exophthalmic goiter, but when compared to the same gland before the remission, it is evident that relatively the histological hypertrophy and hyperplasia is markedly less. The degree of hypertrophy and hyperplasia present depends on the clinical course of the disease, in regard to the remission and exacerbations, either natural or artificial. Involutorial sequelae resembling, histologically, certain benign tumors of the thyroid gland occur following artificial remission, i. e., so-called colloid adenomata and colloid cysts.—Author's Abst.

**Quantity and relation between cholesterine and total fat acids of the blood serum in experimental hyperthyroidism (Sulla quantitaed il rapporto fra colesterina e acidi grassi totali del siero di sangue nell' ipertiroidismo sperimentale).** Sestini (C.), Biochim. e terap. sper. (Milano), 1925, 12, 293-306.

Small quantities of thyroid extract fed for a few days to the rabbit lessens the quantity of fatty acids in the blood serum and increases the cholesterol to a variable extent. Increasing the dosage and the period of feeding causes a decrease in both of these substances. Only large doses over a long period of time can cause hypercholesterolemia. Fatty acids and cholesterol react oppositely in this respect.—P. M. N.

**The treatment and prognosis in myxedema.** Sturgis (C. C.) & Whiting (W. B.), J. Am. M. Ass. (Chicago), 1925, 85, 2013-2017; Abst., A. M. A.

Sturgis and Whiting report their observations on a series of

twenty-six patients, all of whom presented the typical symptoms and signs of myxedema and, in addition, all had a characteristically diminished basal metabolism. Dried thyroid gland (Armour's) was used in all cases. Treatment was controlled by (1) the clinical response of the patient, (2) the basal metabolism, (3) the resting pulse rate, and (4) the body weight. The amount of dried thyroid gland which is necessary to restore the basal metabolism from the initial low point to normal has varied widely, as the total amounts necessary in this series have ranged from 2.3 to 6.5 gm. This variation has been due, in part at least, to the lack of a constant time interval over which the drug has been given. Experience has suggested that sex, age, body weight, duration of the disease, severity of the symptoms, and the initial level of the metabolism bear no accurate or constant relationship to the amount of thyroid gland necessary to restore the patient to a normal condition. In the average adult patient without complications, it has been found that a dosage of 0.13 gm. (2 grains) three times a day can be continued with safety until the basal metabolism and pulse reach normal. With this dosage, the metabolic level and pulse rate usually reach normal in from five to ten days, although individual patients show a wide variation in this respect, and it is advisable, therefore, to keep the patient under close observation and continue with this amount until satisfactory results are obtained. In treating patients with uncomplicated myxedema, it is more satisfactory to confine them in a hospital for from two to three weeks, as this permits close observation and their activity can be controlled. As profound changes occur in the patient's metabolism during the early stages of treatment, it is desirable to keep them in bed for at least a week as a precaution against unpleasant symptoms. If the patient is under observation in a hospital, the initial dosage of 0.13 gm. (2 grains) three times a day is continued until the metabolism and resting pulse rate approach normal and there is clinical evidence of improvement. After thyroid gland has been given in amounts of 0.13 gm. three times a day for three or four days, the first clinical evidence of a thyroid effect is shown by the patients experiencing a sensation of increased warmth, moderate sweating and accelerated mental reactions. Coincident with these changes, there is usually a slight increase in the resting pulse rate, averaging about 10 beats a minute, and, likewise, the basal metabolism shows an average rise of 10 per cent. At this time, the patient's temperature may become somewhat elevated above normal for a few days, the average, however, not exceeding 100 F. The drug should be continued until the basal metabolism is between —10 and —5,

according to the standards of Du Bois. While it is generally accepted that the normal varies between —10 and +10 according to these standards, it has been the author's experience that the average patient with myxedema more nearly approaches a condition approximating normal if the metabolism is maintained between —5 and —10. If the metabolism remains at this level for five or six weeks, there will be a loss of weight which averages from 10 to 15 pounds (4.5 to 6.8 kg.). This loss is due apparently to the disappearance of the subcutaneous, nonpitting edema that is characteristic of the disease. After several months of treatment, it is commonly observed that the patients regain this weight and 5 or 10 pounds (2.3 or 4.5 kg.) in addition, which doubtless results from their greatly improved general nutrition. After the patient's basal metabolism and pulse rate have been restored to normal and there has been evidence of clinical improvement, the second stage of treatment is begun. The object of this time is to determine the exact dosage which will maintain the metabolism at the proper level. This has been called the maintenance dose, and is the amount that is to be taken by the patient each day. This dosage when once established is usually constant and in most instances must be continued throughout a patient's life, although occasionally the size of the dose must be altered, and in very rare instances it appears that there may be complete recovery from myxedema, as the drug may be discontinued without a recurrence of the disease. Most frequently the correct dose is in the vicinity of 0.13 gm. (2 grains) a day, although in individual patients the amount has varied from 0.065 gm. (1 grain) to 0.195 gm. (3 grains) daily. In a study of twenty-five patients with myxedema who have been observed over a sufficient length of time to make results significant, fourteen required a maintenance dose of 0.13 gm. (2 grains) daily; six, a dose of 0.195 gm. (3 grains); two a dose of 0.065 gm. (1 grain), and three, a dose of 0.098 gm. (1.5 grains). Occasionally a patient has taken as much as 0.39 gm. (6 grains) as a maintenance dose for a short period, but this amount has invariably produced symptoms of overdosage if continued for any length of time. There are several complications that may exist in patients with myxedema which make the administration of thyroid gland a somewhat hazardous procedure unless the treatment is very carefully controlled. The complications involve chiefly the heart, kidneys and blood and are observed more frequently in the middle-aged or elderly patients. Illustrative cases are cited.

**Experimental study on the etiology of goiter (Experimenteller Beitrag zur Aetiologie des Kropfes).** Tanabe (H.), *Beit. z. path. Anat. u. z. allg. Path.* (Jena), 1924-1925, **73**, 415.

The authors present the details of the influences of calcium excess and iodine lack on the production of goiter. Selecting rats as the experimental animals a long series of feeding experiments were instituted. Meat, barley and endive constituted the basic ration and to this was added or omitted potassium iodide and calcium salts in varying amounts. The thyroid dimensions and histologic findings are fully tabulated and discussed. The author concludes that his basic diet alone will produce goiter while an unregulated mixed feeding will not; that distilled and tap water are both without influence. He concludes that lack of iodine is the basic etiologic factor and that calcium in appreciable amounts promotes goiter growth only where there is simultaneous poverty of iodine. Very small amounts of potassium iodide are sufficient to inhibit glandular hyperplasia.—A. W. R.

**Hypothyroidism.** Taylor (W. A.), *Northwest Med.* (Seattle), 1925, **24**, 422; *Abst., Am. J. Dis. Child.*, **31**, 124.

The author considers the following conditions due to hypothyroidism. In obesity, dietary restriction usually suffices, but thyroid will hasten the result and is safe if the basal metabolism is watched. In thin, weak, and listless patients with anorexia, minute doses of thyroid are of benefit. Thyroid is of value in young girls with severe dysmenorrhea. Women at the menopausal age with swelling of the hands and feet are helped by thyroid. Colloid goiter and goiter of puberty are usually benefited by thyroid extract, as are long standing cases of exophthalmic goiter which have become hypothyroid. He considers infantile myxedema in the congenital form, in the early form appearing during the first year, and in the mild, attenuated form which is difficult to recognize and is characterized by failure of mental and physical development. The author's dose of dry thyroid extract averages 0.01 gm. for every 6 months of age, minimum dose 0.001 gm., maximum dose 0.05 gm. He recommends alternation of treatment and rest periods.

**Effect of domestication and culture on cranial form and body build (Domestikation und Kultur in ihrer Wirkung auf Schädelform und Körpergestalt).** Weidenreich (F.), *Ztschr. f. Konstit.* (Berl.) 1925, **11**, 1-52.

The thyroid gland is mentioned as being especially connected with certain bodily features as is evident in cretinism.—A. T. R.

# Endocrinology

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THE NEUROLOGICAL AND ENDOCRINOLOGICAL ASPECTS OF ICITHYOSIS, CHRONIC INDURATIVE ECZEMA AND SOME OF THE MINOR FORMS OF SO-CALLED TROPHIC CHANGES IN DERMAL TISSUES\*

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## INNERVATION OF THE DERMAL TISSUES

The skin and its appendages, including the nails, hair and pigment bodies, the pilomotor muscles, and the sweat glands; likewise the subcutaneous tissue and bones, are subject to many changes effected through the vegetative nerves. The subcutaneous tissue and bones belong to what has been termed by some writers the "passive" tissues because of their peculiar lack of secretory and motor function.

The skin and its appendages is supplied by both the sympathetic and the parasympathetic components of the vegetative system. There is sympathetic innervation to all these structures. The parasympathetic innervation, however, is more limited and indefinite except in case of a few body areas.

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\* Read before the Tenth Annual Scientific Meeting of The Association for the Study of Internal Secretions, Dallas, Texas, April 20, 1926.

The preganglionic fibers which pass upward to the cervical sympathetic ganglia carry impulses for vasoconstriction, pilomotor action, sweat secretion, pigment control and the nutrition of the hair of the face and head; also trophic control for the subcutaneous tissue and the bones of the face and head. This is evident from the changes produced by removal of the cervical ganglia. The vasodilator fibers and fibers for sweat inhibition for the face and head come from cranial parasympathetics. As far as known pilomotor action for the face and head depends entirely upon the sympathetics. For the remaining portions of the body, with the exception of the genitalia, vasoconstriction, as well as vasodilatation, pilomotor action and sweat secretion—both activation and inhibition—are due to the sympathetic nerves alone. For the external genitalia the vasodilator fibers and the sweat inhibiting fibers course in the sacral nerve of the parasympathetics.

Vasomotor, pilomotor and sweat reactions are all independent of each other; so we must recognize different systems of neurons presiding over each of these functions.

Aside from the sensory impulses which may be picked up from the skin and its appendages to produce reflex action in dermal structures we have impulses which arise in the internal viscera and also in the higher centers of the brain. These structures are particularly influenced by such emotional stimuli as fear, pain, anger and shame.

Not only are the dermal structures under the influence of the vegetative nerves but they are also subject to the influence of various products of the glands of internal secretion, such as that of the thyroid, pituitary, adrenals and gonads. They also are the possessors of automaticity in action, by which we mean action on the part of the cells themselves without the intervention of nerves or other outside stimuli. Without outside stimuli internal respiration may be carried on and the cells are able to protect themselves from injurious substances which tend to enter through their limiting membranes, and they are able to get rid of substances of a harmful nature which are formed within the cells themselves. Through the nerves and internal secretions, however, their action is integrated and correlated with other structure of the body. There is a very close relationship between the skin and its appendages and certain endocrine se-

cretions. Particularly is this shown in the pigment changes in adrenal insufficiency and at times in pituitary disorders; and more commonly in the changes in the skin and subcutaneous tissue, and the hair in myxedema, and in hypothyroid states of a lesser severity.

#### COMMON PATHOLOGICAL CONDITIONS AFFECTING THE DERMAL STRUCTURES

Dermal structures are subject to many pathologic changes of both hyper- and hypo-active types. Such are vasomotor disturbances; atrophy and hypertrophy of the skin and subcutaneous tissues; dryness, scaliness, induration and fissures of the skin; dryness, early grayness and loss of hair; changes in the nails, and hyper- and an-hydrosis. Hypertrophy and rarefaction of the bones also occur at times. Although the bones do not belong to the dermal structures they are influenced by and through the same vegetative systems.

The explanation of such clinical manifestations is often found in the domain of pathologic changes in the physiologic mechanism of the vegetative nervous system and hyper- or hypo-function of the glands of internal secretion. Many of these pathologic manifestations are of a trophic nature, which fact brings up the question of whether or not there are nerves whose sole function is trophic. Many writers have been satisfied to believe that all trophic changes in these structures can be explained on the ground of changes in the vasomotor nerves, but the argument is raised against this that anemia of the skin, no matter how marked, does not produce atrophy. Anatomy and physiology so far offer no answer to this question, but clinical observation seems to suggest that trophic nerves are a possibility. It is quite probable, however, that trophic changes in these structures may be produced by action directly upon the cells without the intervention of nerves and without changes in glandular secretion, such as that of the thyroid.

In my experience in the treatment of tuberculosis, I have been much interested in the condition of the skin and its appendages. The skin is often dry and scaly, and the hair dry and brittle, with a tendency to fall out and to become prematurely gray. Sometimes pigment changes are present and local atro-

phies are very common. There are also pilomotor manifestations, changes in sweat secretion and alteration in the nails.

Such conditions have usually been ascribed to the fever; but this does not explain. They may be classed, physiologically, as disturbances in the various mechanisms of the skin and its appendages—vasomotor, pilomotor, sweat and trophic; consequently they are representative of an altered function in the vegetative systems which control these structures. Especially are some of these changes found in hypofunction of the thyroid gland. Whether the changes met in tuberculosis are due to hypofunction of the thyroid; or partly this and partly to a disturbance in the vegetative nerves, particularly the sympathetics, and changes in the cells themselves, we are not able to say, for all of these systems show evidence of injury during the course of a long-drawn-out clinical disease accompanied by toxemia. This is not peculiar to tuberculosis, but is found in many states of chronic toxemia and also in states of malnutrition.

This clinical picture, so often met in tuberculosis, led me to become interested in more serious manifestations in the dermal structures. It seemed reasonable that the same underlying pathologic physiology might be present in other dermal afflictions of a trophic nature, such as ichthyosis and chronic eczema.

*Ichthyosis.* Ichthyosis is described as a hypercornification, the skin being susceptible to irritation, eczema and kindred conditions. In patients suffering from ichthyosis the hair of the scalp and brows is usually dry and lusterless. The skin as a rule loses its elasticity, so that at times fissures develop. The subaceous and coil glands of the skin usually show a deficiency in secretion. The skin is dry, scaly, inelastic and thickened.

Ichthyosis usually appears soon after birth, although in some instances it develops later in life. There seems to be a definite hereditary tendency. It has been suggested that the condition was probably due to toxins, and yet there has been no real definite toxin suggested. More recently it has been considered as due to a hypothyroid state, or a disease of the nerves, yet all of these suggestions have been characterized by indefiniteness.

That these dermal manifestations depend upon inherent characteristics of the individual is apparent when it is noted that they usually develop at or soon after birth, and that often

there is a familial relationship as shown in Cases 3 and 5 herein reported.

An interesting and suggestive characteristic of ichthyosis is that it changes with weather. It is usually milder in the summer and more severe during the colder season; in fact, patients suffering from ichthyosis usually stand cold poorly. Sometimes the milder cases entirely disappear during the summer time. This has been ascribed to the fact that the patient perspires in the summer, which moistens the skin and causes it to assume a normal condition; but this increased sweating is more probably simply another evidence of an improvement in the physiological control of these structures in summer.

*Chronic Eczema* is a dermal infection, recurrent in nature, in which there is marked irritability of the skin with itching and induration, and in which the skin sometimes shows marked folding and creasing. There seems to be a hereditary factor in its etiology.

In attempting to assign a cause to such pathological conditions as ichthyosis and the chronic form of eczema, likewise the minor dermal changes herein described as noted in chronic tuberculosis, the relationship to the vegetative nervous system at once forces itself to the fore, because all functions of these structures which are affected are presided over by vegetative nerves. The relationship to weather conditions suggests very definitely the relationship of the disease to those factors which control metabolism, because the disease is worse in cold weather when greater metabolic activity is acquired.

Increased energy requirements in winter is met by increased activity of all those mechanisms which increase energy: the sympathetic nerves become more sensitive and the energizing glands of internal secretion, particularly the thyroid, more active.

It has been pointed out by Kendall that more thyroid secretion is circulating in the tissues in the winter and thus meets the extra energy requirements of the cold. In case of a deficiency in secretion it can be readily understood how this increased demand fails to be met, how metabolism lags and how the patient is unable to supply the extra amounts necessary for maintaining normal conditions in the tissues. As a result the

skin becomes dry, scaly and lusterless, and the patient endures cold badly.

#### REPORT OF CASES

The following cases will illustrate some of the points made in this paper, particularly as regards suggestions of etiology.

*Case I.* K. O., Japanese, aged 17, entered the Pottenger Sanatorium February 6, 1922, suffering from acute caseous tuberculosis, involving both upper lobes, with high fever. He also had a marked ichthyosis which had appeared soon after birth, the skin being dry, thickened and scaly. It resembled the scales of a fish. Large and small scales were continuously thrown off. The patient always suffered from cold.

In spite of active tuberculosis he was put on thyroid, beginning with 1 gr. and increasing to 2 gr. daily. Calcium chloride, 10 cc. of 5% solution, was given once a week from July 16 to October 5, 1925. The patient improved very greatly. The large scales disappeared. The skin did not become entirely smooth but smoother than it had ever been and also somewhat moist. The tuberculosis also improved greatly. The patient formed a small cavity in the right lung and a large cavity in the left. He became fever-free and gained considerably in weight.

*Case II.* F. M. G., aged 68, was suffering from far advanced tuberculosis with cavities in lung, high temperature, also tuberculosis of the larynx with ulceration. He had very marked ichthyosis which had existed from birth. The skin was dry, scaly and was continuously thrown off in large scales. This condition existed over the entire body. He suffered from cold and always wore woolen union suits, even in summer.

He was put on treatment while in the sanitarium—four and one-half months. Thyroid was given, 2 gr. daily, beginning after the patient had been in the sanatorium two weeks. This was continued during his stay except during a two-weeks period when he was having a severe attack of singultus. At the same time he was given calcium chloride, 10 cc. of 5% solution, every four days. He improved very greatly. The scales almost entirely disappeared from the body; the skin became quite smooth and somewhat moist, and the patient declared that it was the first time he had had any relief during his life.

*Case III.* J. R., aged 28, had dry scaly skin since birth, being worse in winter than in summer. Face and hands chapped easily during cold weather. There was no itching. On exposure to the sun the skin burned and blistered easily but did not tan.

*Family History.* The father's height was 6 feet; weight, 210 pounds; his skin was soft. The mother was 5 feet 10 inches in height, and weighed 220 pounds. Her osseous system was well developed. Her skin had a tendency to dryness. One brother died of pneumonia; one died from accident at 3½ years. One brother, aged 15, has dry scaly skin; one brother, aged 21, has scaly skin on exposed surfaces; one brother, aged 27; one sister, aged 25, and one sister, aged 9, all have a slight tendency to dryness.

Physical examination of the patient showed skin uniformly dry and scaly over the entire body, with some small indurated folds on flexor surface of the arms. Scales in the nature of thin white flakes show both on exposed and unexposed surfaces. The hair was coarse but not unduly dry, and the scalp scaly.

The patient was suffering from extensive far advanced tuberculosis with cavities and fever.

*Medication.* Thyroid, 1 gr. daily for two months and 2 gr. daily for six months, together with calcium chloride, 10 cc. of 5% solution every four days during entire period—eight months, were administered. The skin condition improved markedly and at present it is soft and smooth and shows practically no scaling.

*Case IV.* J. F., aged 24, suffered from asthma up to the age of 17 years. He entered the Pottenger Sanatorium, suffering from moderately active tuberculosis, May 21, 1925. He was discharged February 27, 1926. His skin over both exposed and unexposed parts of body had always been dry and leathery. The eyebrows were scanty. He stood cold badly. On account of the dryness and scaliness of the skin he had always been sensitive.

He was treated by thyroid and calcium chloride; thyroid, 1 gr. daily from June 21, 1925, to August 29, 1925; 2 gr. daily August 29 to December 1, 1925, and 3 gr. daily from December 1, 1925, to date of discharge, February 27, 1926. He is still taking it. Calcium chloride, 10 cc. of 5% solution was given every four days from July 13, 1925, to February 27, 1926.

The skin improved very markedly. The scales disappeared; the skin became soft and moist, and the surface looked about the same as those of ordinary individuals. This was the first relief the patient had had since this condition started as a child.

*Case V.* Mrs. G. H., aged 26, began having trouble with her skin at the age of 11. This took the form of inflammation with induration and itching, confined to arms and neck. The first attack lasted one year. At the age of 16 she was troubled with the condition from June to December. She had had two x-ray treatments a week in mild doses and improved. At the age of 21 the trouble returned and persisted for some time, beginning with papules which broke, forming pustules and scales. The lesions were very changeable: Sometimes only redness with intense itching; at other times, induration. She scratched lesions in sleep and caused excoriation of the skin. Keeping the arm under the bed covers or protected by clothing increased the symptoms. She always noted that the symptoms were worse when she was nervous and at the menstrual periods. From June to December, 1921, she took 18 x-ray treatments without improvement. These resulted in burns of the skin with telangiectasis. She noticed that the condition was always worse in winter.

I first saw the patient May 1, 1923, at which time the skin over the face and flexor portions of the arms was very thick and thrown into folds. Itching was extremely intense. The skin was dry, scaly and leathery. Excoriations from scratching were present on the arms from the elbow to the wrist. The vessels of the face and arms were dilated as a result of x-ray treatment. She showed scantiness of the external third of the eyebrows and a dry skin over the body; she withstood cold badly, giving the impression of a definite hypothyroidism. She also had a tendency to hay fever.

*Family History.* Her father was 6 feet tall and weighed 190 pounds. He had a large frame and was always active. There was no early grayness. He died of heart trouble at 53. The mother's height was 5 feet 8½ inches; weight, 182 pounds. She was of large frame but did not appear fat. She had no skin trouble. One brother was 5 feet 5 inches tall and weighed 170 pounds at the age of 42. A sister was 5 feet 5 inches tall and weighed 142 pounds at the age of 39. They had no skin abnormalities. The patient has one child 3 years old who weighs 40½ pounds. She has a slight tendency to dryness of the skin and itching. The condition improved following the use of thyroid. The difficulty returned in cold weather but yielded again to increase in the amount of thyroid.

*Menstrual History.* The patient was regular until 1925. Since then she has flowed every 18 days. The skin condition was a little worse toward end of the period.

*Treatment.* Desiccated thyroid was given, 1 gr., daily from May 1 to May 14, 1923; 2 gr. daily from May 14, 1923, to February 4, 1924. This seemed to relieve the condition very satisfactorily until February. From February 4 to March 13, 1924, 3 gr. daily was given. With this dosage the skin cleared and became soft and pliable, but showed signs of recurrence in March, 1924. Four gr. daily was given from March 13 to March 27, 1924, when the patient began to experience slight tremors. Thyroid was then withheld for a short period and then resumed with 3 gr. daily, which amount the patient has taken until the present time. She was also given calcium chloride, 10 cc. of 5% solution, from 2 to 3 intravenous injections a week, from May 1, 1923, to March, 1924. Calcium injections were stopped from March, 1924, to March, 1925. In the spring of 1925 two injections a week were given, and during February and March, 1926, one injection a week was given. Since March, 1923, calcium lactate (20 gr. daily) has been taken by mouth.

As a result of the treatment the skin condition has been markedly improved; the skin has become more moist; the itching decreased and shortly disappeared entirely. The induration has also gradually disappeared, and at the present time the skin shows little evidence of former induration. The thickness which is present is accentuated by the results of the x-ray treatment. Also the excessive nervousness has disappeared. It was noted on September 12, 1923, that the patient had gained 3½ pounds in weight. Hair was then present and normally distributed over the forearms, and the skin had lost much of its leathery appearance. March 26, 1926, except for slight relapses during the winter months each year, the patient has remained in a very satisfactory condition. These relapses quickly disappear under an increased amount of thyroid and the resumption of the intravenous injections of calcium chloride.

#### DISCUSSION

In the treatment of the above cases ointments and soothing baths, which are usually employed, were purposely omitted. This was an experiment to determine if those measures that are known to influence the neurocellular mechanism presiding over these dermal tissues would produce a favorable response. The manifest difficulties surrounding the treatment of these patients will be evident to all. Part of them were suffering from far-advanced, active tuberculosis. All but one had tuberculosis. Furthermore, the prolonged toxemia had a tendency to cause conditions similar to the ones that we were trying to treat. Foods containing large quantities of calcium should be employed during treatment, and the proteins, which hasten its elimination, should be avoided; but in tuberculous patients such a diet could not be followed. There is no doubt that the improvement in the patient's general condition had some influence in causing the

skin lesions to respond, but that it was not the main factor is made clear by the fact that in all instances the skin afflictions were present prior to the time the patient had tuberculosis.

I cannot believe that these dermal afflictions are purely hypothyroid in nature; for, if they were, we would expect a more complete yielding to the administration of thyroid preparations than occurs. In other instances of thyroid deficiency, even cretinism and myxedema, there is a more rapid and more complete response. In case of the patients reported herein, however, the response was not complete in a single instance. We found that thyroid alone would not keep the skin in as good condition as thyroid with calcium added. This was noted even though the thyroid was pushed to the point of causing increased heart action and nervous instability. We also found that while calcium by the mouth, which was given between the series of intravenous injections, was advantageous, it had to be supplemented ever now and then by intravenous administration, especially when relapses occurred. A point indicative of the intimate part played by the nerves is the fact that all of the various mechanisms, trophic, sweat, vasoconstrictor, pilomotor, and even the subcutaneous fat distribution are affected.

The relapses occur during times of nerve stress and when the weather becomes cold. The former are times when nerve imbalance is accentuated; the latter when thyroid deficiency shows most markedly and the calcium content of the cells is relatively low. So it seems justifiable to assume that these lesions do not represent a pathologic condition of one phase of vegetative control to the exclusion of others, but rather a general disturbance in all: the nerves; the endocrine organs, particularly the thyroid; and the automaticity of the cell itself, particularly as it depends upon its ionic content, its permeability and reactivity.

We note that these mild instances of dryness and scaliness of the skin which are met in chronic tuberculosis improve when the patient's nutrition improves and the general physiologic balance is restored. We assume that nerve, endocrine and cell balance are all improved when this condition has been attained. We also at times see the hair become oily and even regain some of its color when health has been regained. The vasoconstrictor and sweat anomalies met in patients suffering from a long-drawn-

out toxemia also disappear with recovery. That these lesions are in part due to the general process of wasting in tuberculosis may be true; but it is desirable to define them more accurately if possible, and this may be done by a careful study of their physiologic control. It is possible that there is a close etiological relationship between these minor changes noted in tuberculosis and the more severe lesions represented by ichthyosis and chronic eczema cited above, even though the former is apparently caused by a disease process while the latter is apparently due to inherited factors.

## NON-DIABETIC GLYCOSURIA

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A light or even a heavy glycosuria is not an uncommon finding in the routine examination of patients. In Table I, I have collected references to such findings as have been reported by various observers in the recent literature. Noteworthy among these observations are those in which the condition had been observed over very prolonged periods, viz., from 3 to 35 years.

Various terms have been applied to this non-diabetic type of glycosuria. Thus it has been called diabetes innocens; renal diabetes; renal glycosuria. Such terms as the last two of these are misnomers since glycosuria is always renal, being dependent upon the renal threshold as well as the glycemic level. Glycosuria innocens is a better term since it indicates at least the non-diabetic character of the glycosuria—but for this very reason, since whenever glycosuria is present it is imperative to determine whether or not it is due to a diabetic condition, I have adopted the term *non-diabetic glycosuria* as most applicable to glycosuria of this type.

I shall not review the rather extensive literature on this subject as it is sufficiently covered in the references included in the table. My only object in this report is to add my personal observations to those which have already been reported by others, thus adding further confirmation of the observation that the non-diabetic type of glycosuria has no pathological significance, moreover not only does it require no treatment but no treatment is of any avail. These patients may secrete more or less sugar for many years, without any ill effects. The only important point in these cases is to be sure that the glycosuria is of the non-diabetic type and not due to an early stage of diabetes, for while in the former case no treatment is required, in the second, treatment is vitally essential. It is therefore important to review the necessary steps for the establishment of the correct diagnosis.

A diagnosis should never be based on the presence of glyco-

suria alone, for it is imperative to establish its significance beyond a doubt. Therefore, when the presence of glycosuria is observed, a fasting blood sugar determination and a careful urine examination should be made at once. If the fasting glycemia is above 160 mg. per 100 cc. one may be fairly certain that one is dealing with a case of diabetes. As further confirmation of this supposition, the patient should be instructed to eat a heavy breakfast of pancakes with an abundance of syrup, the blood and urine being examined two and one-half hours

TABLE I  
Summary of Observations of Various Authors on Non-Diabetic Glycosuria

Author	Age of Patient at Beginning of Treatment	Sex	Period of Observation	Daily Sugar Output
Parkes, Weber T.	.....	F	35 years	30 gms.
Holst, J. E.	24 years	M	23 years	
Holst, J. E.	7 years	M	22 years	1%
Labbé, M.	6 years	..	19 years	
Allan, Wm.	17 years	F	18 years	
Johnsson, A.	28 years	F	16 years	16- 49 gms.
Johnsson, A.	.....	F	16 years	
Bailey, C. V.	.....	F	11 years	20 gms.
Garrad, A. E.	8 years	F	11 years	
Labbé, M.	6 years	F	11 years	
Johnsson, A.	25 years	M	10 years	1.2-0.03%
Johnsson, A.	.....	M	10 years	
Garrad, A. E.	12 years	M	9 years	
Paullin, J. E.	16 years	M	7 years	34 gms.
Lemann, I. I.	15 years	M	6 years	Traces
Lewis, D. S.	.....	..	5 years	25 gms.
Lewis, D. S.	.....	..	5 years	16 gms.
Lemann, I. I.	4 mos.	M	3 years	Traces
Faber, K. and Norgaard, A.	26 years	F	3 years	60- 80 gms.
Marsh, P. L.	22 years	F	1.3 years	50- 60 gms.
Marsh, P. L.	.....	..	1.25 years	15-122 gms.
Lemann, I. I.	19 years	M	1 year	Traces
Marsh, P. L.	74 years	M	.....	30- 50 gms .
Goldbloom, A.	20 mos.	M	.....	1%

later; if at that time the blood sugar is normal, even though the fasting blood sugar may have been between 160 and 180 mg. per 100 cc., diabetes can be ruled out, for, if diabetes be present, two and one-half hours after such a heavy carbohydrate breakfast the patient will certainly show a more or less pronounced hyperglycemia. One can go a step further, especially if the data are not clearly defined, and make a glucose tolerance test in the following manner. A sample of fasting blood is taken, after which the patient is given an ice-cold solution of 100 gm. of glucose dissolved in from 250-300 cc. of water, to which the juice of one lemon has been added. Samples of blood

and urine are taken at periods of one-half hour, one hour, and two, three and four hours after the glucose is administered. Even though the fasting blood sugar may be normal, if the patient is diabetic the blood sugar curve will show a slow and prolonged rise with an equally prolonged fall, so that even four hours after the ingestion of the glucose it will not have returned to the normal level. On the other hand, in a non-diabetic individual the blood sugar curve will show a quick rise with an equally abrupt fall, so that in one, or at the most in two, hours after the ingestion of the glucose the curve will return to the normal level. In certain cases the blood sugar content may not show any increase at all, indicating that the individual in question has a very strong tolerance for carbohydrates, that the islands of Langerhans secrete an unusually abundant supply of insulin. By this method, therefore, one can differentiate between the diabetic and the non-diabetic types of glycosuria, and, moreover, in this manner the renal threshold for sugar can be determined, a point which is not only of scientific interest but is also of practical importance for the interpretation of our findings.

However, our observation of the patient with a non-diabetic type of glycosuria should not stop with a single examination, for, as stated above, a true non-diabetic glycosuria remains practically the same as to the sugar content of the urine whatever the diet of the individual—and a series of examinations are needed to determine whether or not this is true in any individual case.

Final conclusions regarding the validity of our belief that non-diabetic glycosuria is truly innocent in character demand prolonged observations of a series of cases, and therefore in Table II, I am submitting my own observations on a group of eight cases for periods of from two to eleven years. In none of these cases was the glycosuria marked, but in all of them the glucose tolerance tests showed a low renal threshold, which accounts for the post-prandial glycosuria. These patients simply "spill" sugar after heavy meals and thus lose small quantities of sugar each day. This loss is of little consequence, however, when we consider that a normal person ingests some 400 gm. of carbohydrates daily in addition to the carbohydrates derived from protein and from fat, so that even if he loses from four to six grams through the urine, this is but a mere

trifle in comparison with the amount of carbohydrates which he utilizes. Moreover, the loss may be disregarded, for it cannot be stopped; there is at present no means whereby the renal threshold may be raised so that the sugar may be retained.

TABLE II  
Non-Diabetic Glycosuria  
(Author's Series)

	Age When Glycosuria Was Discovered	Sex	Length of Time Cases Have Been Under Observation
I	32 years	M	7 years
II	30 years	M	11 years
III	16 years	M	5 years
IV	46 years	M	10 years
V	44 years	M	2 years
VI	34 years	M	6 years
VII	17 years	F	7 years
VIII	2½ years	M	5 years

A brief review of the histories of the cases reported in Table II may be of interest.

*Case I.* (109856) A man, 34 years of age. There was no familial history of diabetes. He had been married for ten years and had three children living and well. He had had none of the usual diseases of childhood. He came to the Cleveland Clinic because of his glycosuria, which had been discovered in the course of an examination for life insurance. Because of this finding he had been treated by his family physician for diabetes.

A glucose tolerance test made two years before I first saw him had given the following information:

Bl. Sug. mg./100 cc.	Fasting	Time after ingestion of glucose		
		½ hr.	1 hr.	2 hrs.
Urine Sugar	110	75 gm.	195	200
	0	glucose by mouth	2+	3+

When I first saw him on January 24, 1922, he had a fasting blood sugar of 128 mg. per 100 cc. and no glycosuria. A glucose tolerance test gave the following results:

Bl. Sug. mg./100 cc.	Fasting	Time after ingestion of glucose			
		½ hr.	1 hr.	2 hrs.	3 hrs.
Urine Sugar	128	100 gm.	207	146	125
	0	glucose by mouth	2+	1-	0

Total water intake 850 cc.

Total urine output 850 cc.

Plasma Cl. 655 mg./100 cc.

Bl. Urea 33 mg./100 cc.

Bl. Creatinin 1.8 mg./100 cc.

Bl. Uric Acid 3.5 mg./100 cc.

Bl. N. P. N. 25.2 mg./100 cc.

Bl. Wassermann negative.

These findings made it appear that this was a case of non-diabetic glycosuria. The summary of observations in this case to February, 1924, is as follows:

	1920	1921	1922	1923	1924
Date		Jan. 24	Feb. 14	May 24	Nov. 1
mg./100 cc.	110		128	104	102
Urine Sugar	1+	0	1+	0	1+
			1926		0
Date		Feb. 17	March 22		
Bl. Sug. mg./100 cc...		87		78 (1½ hrs. P. C.)	
Urine Sugar .....		0		3+	

Another glucose tolerance test made on February 12, 1924, gave the following results:

	Fasting		Time after ingestion of glucose				
			½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug.		100					
mg./100 cc.	85	mg.	146	191	117	78	53
Urine		glucose					
Sugar	0	by mouth					
Total Water intake	875 cc.						
Total urine output	386 cc.						
Total sugar intake	100 gm.						
Total sugar output	1.54 gm.						
Plasma Cl.	585 mg./100 cc.						
Bl. Urea	39 mg./100 cc.						
Bl. Uric Acid	2.3 mg./100 cc.						
Bl. Creatinin	1.1 mg./100 cc.						
Bl. N. P. N.	42.6 mg./100 cc.						
Bl. Plasma acetone	negative.						

*Case II.* (116819) A man 36 years of age. One sister and one brother had diabetes. He had two children, living and well. He had had no illness in childhood or later. He came to the Cleveland Clinic because of glycosuria which had been discovered in 1916 in an examination for life insurance. Because of this finding insurance had been refused. He had had rather frequent urine examinations during the preceding six years, sugar being found repeatedly.

When I first saw this man on September 19, 1922, his urine showed no sugar and his blood sugar 4½ hours after a meal was 114 mg. per 100 cc. A glucose tolerance test on the next day gave the following results:

	Fasting		Time after ingestion of glucose				
			½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. sugar		100					
mg./100 cc.	97	gm.	113	119	93	63	84
Urine		glucose					
Sugar	neg.	by mouth					
Total water intake	920 cc.						
Total water output	960 cc.						
Total sugar intake	100 gm.						
Total sugar output	0.234 gm.						
Plasma Cl.	595 mg./100 cc.						
Bl. Urea	15 mg./100 cc.						
Bl. Uric Acid	2.3 mg./100 cc.						
Bl. Creatinin	1.2 mg./100 cc.						
Bl. N. P. N.	21 mg./100 cc.						
Plasma acetone	negative.						
Blood Wassermann							

These data showed clearly that we were dealing with a renal type of glycosuria, that is, with a very low renal threshold for sugar, lying somewhere between 119 and 93 mg. per 100 cc. The patient, therefore, would not fail to show glycosuria almost constantly as had been the case during the preceding six years. The data on this case are summarized below.

Date	1916	1917	1918	1919	1920	1921	1922		1924	1925	1926	
							Sept. 19	Sept. 20	April 9	Feb. 2	Jan. 4	Jan. 5
Bl. Sug. mg./100 cc. Fasting.....							114*	97	110†	89†	92§	
Urine Sugar.....	1+	1+	1+	1+	1+	1+	0	0	0		0	1+

\* 4 1/2 hours after eating.

† 4 hours after eating.

§ 2 1/2 hours after eating.

*Case III.* (122143) A boy 17 years of age. No familial history of diabetes. He had had measles and whooping cough in childhood, chickenpox a year before, a severe attack of mumps at the age of 12. An appendectomy had been performed when he was six years old and a tonsilectomy at the age of seven years. As he had been told he had diabetes he came to the Clinic in March, 1923, giving the following history:

In August, 1922, he had had a bad cold. At that time sugar was found in the urine but he had no clinical symptoms of diabetes. Repeated examinations of the urine occasionally showed sugar but a blood sugar examination had never been made.

When I first saw this patient on March 26, 1923, the urine contained sugar—3 plus—and the fasting blood sugar was 89 mg. per 100 cc. The following day I made a glucose tolerance test with the following results:

	Fasting	100 gm.	Time after ingestion of glucose				
			1/2 hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	84	100 gm.	113	84	98	79	84
Urine Sugar	0	glucose by mouth	0	0	0	0	0
Total water intake	975 cc.						
Total urine output	363 cc.						
Plasma Cl.	575 mg./100 cc.						
Bl. Urea	24 mg./100 cc.						
Bl. Uric Acid	2.0 mg./100 cc.						
Bl. Creatinin	0.91 mg./100 cc.						
Bl. N. P. N.	28 mg./100 cc.						
Plasma Acetone	negative.						

No glycosuria occurred during the test, although on the preceding day it had been 3 plus. The tolerance test showed clearly that this boy did not have diabetes. The data in this case may be summarized as follows:

Date	1922	1923	1926
	March 26	March 27	Feb. 17
Bl. Sug. mg./100 cc.		89	84
Urine Sugar	1+	3+	0

*Case IV.* (106174) A man 50 years of age. No familial history of diabetes. He came to the Clinic because of glycosuria, which had been discovered in 1917 in the course of an examination for life insurance. Repeated examinations of the urine during subsequent years failed to show glycosuria except once, in 1921. On account of this history I made a glucose tolerance test on September 13, 1921, with the following results:

	Fasting		Time after ingestion of glucose				
			½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.		100 gm.	183	180	137	88	64
Urine Sugar	112	glucose by mouth		1+	1+	1+	0
Total water intake	900 cc.						
Total urine output	1105 cc.						
Blood Wassermann	negative.						

These results definitely demonstrated that we were dealing with a non-diabetic glycosuria in which the renal threshold to sugar lay somewhere between 137 and 88 mg. per 100 cc.

The glycemia-glycosuria history in this case to date may be summarized as follows:

Date	1917	1921	1924				1925				1926 Jan. 5
			Sept. 13	Mar. 16	Sept. 2	Dec. 9	Mar. 20	July 1	Oct. 20		
Bl. Sug. mg/100 cc.			112								56
Urine Sugar .	1+	1+	0	0	0	0	0	0	0	0	0

*Case V.* (137141) A man 44 years of age. No familial history of diabetes. He had had measles, mumps, chickenpox, diphtheria, scarlet fever and whooping cough in childhood, and later in life he had had influenza and amebic dysentery in 1914, while in China. He was married and had four children, living and well. He came to the Clinic because of glycosuria, which had first been discovered six weeks before in the course of an examination for life insurance. In repeated examinations during the following few days the urine sometimes showed sugar and sometimes was sugar free. At that time his fasting blood sugar was 120 mg. per 100 cc. A glucose tolerance test which was made on April 10, 1924, in Baltimore, gave the following results:

	Fasting		Time after ingestion of glucose		
			½ hr.	1 hr.	2 hrs.
Bl. Sug. mg./100 cc.		100 gm.	216	180	142
Urine Sugar	117	glucose by mouth		1+	1+
Total sugar output	0.845 gm.				

This patient came to see me on June 4, 1924, at which time I repeated the glucose tolerance test with the following results:

	Fasting		Time after ingestion of glucose				
			½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.		100 gm.	183	163	104	70	59
Urine Sugar	84	glucose by mouth		1+	tr.	0	0

Total water intake 950 cc.  
 Total urine output 850 cc.  
 Total sugar intake 100 gm.  
 Total sugar output 0.17 gm.  
 Plasma Cl. 585 mg./100 cc.  
 Bl. Urea 24 mg./100 cc.  
 Bl. Creatinin 1.1 mg./100 cc.  
 Plasma Acetone negative.  
 Blood Wassermann negative.

The above and the following glucose tolerance test, made in California on February 9, 1926, showed that the glycosuria was of non-diabetic origin:

	Fasting		Time after ingestion of glucose				
			½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	95.2	100 gm.	133.3	150	74	55.5	83.3
Urine Sugar	0	glucose by mouth	0	1+	0	0	0

This is really a case of non-diabetic glycosuria of the spasmoid type with a renal threshold for sugar somewhere between 163 and 104 mg. per 100 cc. This low renal threshold, as stated above, was demonstrated by a glucose tolerance test made in California on February 9, 1926, in reference to which the patient made the following statement: "You may be interested to learn that I have made no attempt to limit my diet in any way. Last week I tipped the scales at 145 pounds and am feeling better than I have felt for years."

The history of this case may in turn be summarized as follows:

	1924	1925	1926
Date	Apr. 10	June 4	Mch. 19
Bl. Sug. mg./100 cc.	117	84	85
Urine Sugar	1+	0	0

*Case VI.* (103131) A man 34 years of age. His father and his father's brother had died of diabetes and one brother had severe diabetes. He had been married 11 years and had two children, living and well. He had had none of the diseases of childhood, but some years before had had a gonorrhreal infection. He came to the Clinic because of glycosuria, which had been found in the course of an examination for life insurance. On account of the marked familial history of diabetes, the presence of glycosuria was naturally interpreted as being due to diabetes.

I first saw this patient on May 28, 1921, when his postprandial blood sugar was 110 mg. per 100 cc. As a urine examination on May 31st showed a considerable reduction with Benedict's solution, a glucose tolerance test was performed on June 4th, with the following results:

	Fasting		Time after ingestion of glucose				
			½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	111	100 gm.	151	145	77	77	88
Urine Sugar	2+	glucose by mouth		2+	2+	1+	1+
Total water intake	900 cc.						
Total urine output	178 cc.						
Total sugar intake	100 gm.						
Total sugar output	0.206 gm.						
Plasma Cl.	490 mg./100 cc.						
Blood Urea	14.4 mg./100 cc.						
Blood Wassermann	negative.						

\* 2 1/4 hours after eating.

It was clear that in this case also we were dealing with a non-diabetic type of glycosuria.

The history may be summarized as follows:

		1921	1926
Date		May 28	May 31 June 4 Jan. 9 Jan. 26
Bl. Sug. mg./100 cc.		110	111 88

Urine Sugar            2+            2+            2+ neg. neg.  
*Case VII.* (104930) A girl, 18 years of age. No familial history of diabetes. She had not menstruated for 18 months. A tonsilectomy had been performed three years before. She came to the Clinic because of glycosuria, which had not been eliminated even by prolonged dietary restriction.

No clinical symptoms of diabetes accompanied the onset of the glycosuria, which had been first observed in 1920. She had been on practically a starvation diet for two weeks before I saw her, as the result of which her weight had fallen from 123 to 83 pounds, so that she looked like a skeleton and was so weak that she could hardly stand up. Physical examination revealed nothing of significance except the emaciation.

When I first saw this patient on July 27, 1921, glycosuria was present and her blood sugar content was 125 mg. per 100 cc. The following day I made a glucose tolerance test with the following results:

	Fasting	Time after ingestion of glucose			
		½ hr.	1 hr.	2 hrs.	3 hrs.
Bl. Sug.	100				
mg./100 cc.	84 gm.	131	141	102	84
Urine	glucose				
Urine Sugar	1+ by mouth		1+	1+	1+
Total water intake	950 cc.				
Total urine output	74 cc.				
Total sugar intake	100 gm.				
Total sugar output	0.103 gm.				
Blood Wassermann	negative.				
P. S. P. 55/15 (2 hours).					
R. B. C.'s	3,590,000.				
Hgb.	65%.				
W. B. C.	9400.				

These data showed clearly that we were dealing with a pure type of non-diabetic glycosuria, this conclusion being confirmed by subsequent observation, for no matter how heavy the carbohydrate content of the diet was made the blood sugar was not increased, though the glycosuria continued. This girl is now in perfect health.\*

For subsequent data, see next page.

In certain cases in which glycosuria has been demonstrated repeatedly it seems eventually to clear up, although in such cases one should bear in mind that the urine may have been examined at intervals when it was sugar-free. One must remember that in many cases the glycosuria is post-prandial. This is well illustrated by the case of a little boy 3½ years of age (Case VIII, 124313), in which, during 1922, glycosuria was found repeatedly by his family physician. A low diet was prescribed, in spite of which the boy continued to show glycosuria

\* For full report of this case see J. Am. M. Ass., 1922, 78, 103.

Subsequent data, Case VII. See page 123.

Date	1920	1921					
		July 27	July 28	Aug. 4	Aug. 5	Aug. 6	Aug. 8
Bl. Sug. mg/100 cc.....		125	84				100
Urine Sugar.....	1+	1+	1+	0	0	0	1+
Date	1921						
	Aug. 9	Aug. 10	Aug. 11	Aug. 12	Aug. 13	Aug. 17	Aug. 22
Bl. Sug. mg/100 cc.....				81			75
Urine Sugar.....	1+	0	0	0	0	1+	
Date	1921				1924 Oct. 10	1926 Jan. 27	
	Aug. 23	Sept. 13	Oct. 4	Nov. 5			
Bl. Sug. mg/100 cc.....		73	77	129	122*	95	
Urine Sugar.....	1+	0	0		0	0	

\* 3 hours after eating.

frequently, although there were periods during which he was sugar-free. In the belief that he was dealing with a diabetic condition the physician brought the boy to me on June 27, 1923.

There was nothing of significance in either the family or the personal history and the boy seemed perfectly well, the only abnormal finding being the glycosuria.

The summary of the findings, which is given below, shows that the blood sugar data are quite normal, so that diabetes can be definitely ruled out. The lad has remained in perfect health up to the present time without dietary restriction.

	1922	1923			1925	1926
Date	June 11	June 29	June 30	July 2	July 5	May 29
Bl. Sug. mg/100 cc.				143	93	59
Urine Sugar	1+	1+	0		tr.	0

#### CONCLUSIONS

1. Eight cases of non-diabetic glycosuria which are reported in this paper have been observed over periods ranging from two to eleven years, during which time the patients have not had diabetes.

2. These patients have had a full diet throughout the periods that they have been under observation.

3. The ages of these patients ranged from 2½ to 44 years at the time the glycosuria was discovered.

4. The literature on non-diabetic glycosuria includes reports of cases for varying periods up to 35 years, throughout which a normal status was maintained.

5. The highest daily excretion of sugar in the cases reported in the literature was 30 grams per day.

6. Observations of non-diabetic glycosuria show that it is an innocent anomaly requiring no restriction of diet or other treatment.

7. The importance of repeated examinations in cases of glycosuria which is supposed to be non-diabetic in character is emphasized, as is the necessity of glucose tolerance tests, in order to make sure that the glycosuria is not due to diabetic or a prediabetic condition.

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# TREATMENT OF SENILE CATARACT WITH THYROID EXTRACT\*

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The medical treatment of senile cataract has interested ophthalmologists for at least a hundred years. A voluminous literature has accumulated and, in spite of much empiricism in treatment, a few noteworthy observations have been recorded. Aside from a small group of cases in which cataracts develop upon the basis of physical agents, such as intense light and heat, and trauma to the lens or adjacent structures, it is apparent that the common type of cataract is more intimately associated with general bodily disturbances. This disturbance is apparently related to metabolic changes as noted in the juvenile with tetany with probable alterations of the calcium balance, especially noted in endemic goitrogenous regions. Whether the parathyroid or thyroid glands are at fault is not clearly understood. Then we find a group of cases where the changes in the lens, and other structures of the eye, are associated with diabetes and frequently improve as the diabetes is brought under control. By far the largest group of cataract cases, however, is observed in individuals past fifty years of age, and are spoken of as senile cataract. The cataracts are of various types depending upon the location in the lens. These cataracts are practically always bilateral, one eye usually showing the process somewhat more advanced than the other, therefore indicating a general rather than a local cause. In this group also there may, from time to time, be variations in the cataract, depending upon the general health. Regression without treatment may be noted and the opacities may be stationary for years.

The individuals in whom the opacities appear show the bodily changes which are commonly called the signs of old age. The bodily changes are referable to all the embryonic tissues, but

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those most readily observed are in the epidermal structures. The hair is usually thin, gray, dry and brittle; the eyebrows are thin, especially in the outer half, and tending to the formation of long bristles; the cilia are thin or wanting; the eye shows arcus senilis; the lens presents cataract. The bodily hair, especially in the axillary and pubic regions, is thin. The skin is dry and wrinkled, frequently thickened, and the sweat glands function poorly. The teeth show early destruction and loss. Keratosis, carcinoma baso-cellulare and epitheliomata are common. The nails are ridged longitudinally and are thin and brittle. In these individuals the mentality shows some impairment. The cardiovascular system is frequently the site of degenerative disease. The osseous system shows changes in the joints, particularly with the formation of Heberden's nodes, and chronic arthritis. The gastrointestinal tract may present disturbances associated with lack of hydrochloric acid in the stomach or there may be constipation. Renal impairment may be observed. Other conditions found in this group are reduced function of the internal secretion of the pancreas in diabetes; the formation of gall stones, diminished libido and many other disturbances generally associated with old age. It is also in this group that carcinoma appears to be more frequent.

Studies on the metabolic rate show very little to indicate that the metabolism, as represented by the oxygen-carbon dioxide exchange, is materially altered, although such individuals suffer from the cold. The present chemical studies on blood and urine show very little alteration from the normal, except in those cases with diabetes or renal disease. The calcium, magnesium, potassium, sodium and cholesterol metabolism need further study.

The changes in the ductless glands are not constant nor striking, but disturbances of function of single glands and alteration of balance of the related glands may be observed. The general bodily disturbances may be related to structural and functional changes in one or more of the ductless glands or the changes in these glands may represent only a part of the general picture of pathological old age.

We are indebted to Pollock (1923) for many of the early references on the medical treatment of cataract. In his review of the literature, the French are shown to have had the greatest enthusiasm in carrying out local and general medical measures

for treatment. Gondret (1829), is given credit for being one of the first to report the use of iodine preparations in the treatment of senile cataract. He used potassium iodide in large doses internally, alone and with tonics, and reported successful results. Others who followed used iodine or iodine salts in various ways, and also claimed improvement, and even cures in some cases. Notable among these early authors were Arlt (1854), who used an ointment containing potassium iodide, applied around the eyes; and Martin (1863), who employed iodides in eye lotions and drops.

In 1902 Würdemann reported three cases cleared by general treatment. Badal (1901), and in subsequent papers reported the control of opacities by eye baths, drops and lotions of potassium and sodium iodide and the subconjunctival injection of potassium iodide. He stressed the importance of early treatment. The injections were later used by Verderau (1904, 1906), DeWecker (1905), Boisseuil (1906), and von Pflugk (1906, 1908), but, although reported as successful, were later abandoned because of the pain of the procedure. There was some doubt whether the iodine could penetrate the lens, but its presence in the aqueous and vitreous humours which bathe the lens was demonstrated by Badal's assistants. Later von Pflugk (1908), presented experimental evidence that iodine could enter the lens after subconjunctival injection of potassium iodine solutions.

Von Pflugk (1906) gave a two-weeks' course of potassium iodide injections in various places around the cornea, followed by a course of dionin drops and a repetition of the course of injections. Wilkinson (1906) employed lithium and potassium iodide with tonics of iron and quinine and found no marked deterioration of vision under such treatment. In 1911 and 1913 Dor recommended baths of sodium iodide and calcium chloride based upon the assumption that nascent calcium iodide, if present, would be beneficial. He reported encouraging results in cases where the vision was not impaired more than one-half. Kaz (1912, 1914) reported successful results with Dor's method.

Schmidt-Rimpler (1908) used potassium iodide ointment and suitable glasses and felt that the opacities failed to advance in certain cases. Chevallereau (1912) reported further successful results with iodide eye baths and lotions.

Nepper (1908) and Connor (1909) reported improvement after dionin. Other substances used, about this time, with reported success were lens albumin by mouth by Römer (1908); lens extract by subcutaneous injections by Davis, thiocyanate by mouth and subcutaneous injections by Bernard (1909); resorcin by Elze (1909); mercury cyanide, one in four thousand, subconjunctivally, by Smith (1912) and Harry (1912); ion-iodide-electricity by Juan De Arana (1916) and Jones (1916) and others.

Koster (1913) used radium locally, probably in the treatment of secondary cataract. From 1918 to 1920 Cohen and Levin (1920) studied the effects of radium on cataract and reported improvement in 87 per cent of the cases. Franklin and Cordes (1920) found improvement in 84 per cent of cases after the use of radium.

Green and Green (1919) reported 58 per cent of improvement after using the Smith method of subconjunctival injections of mercury cyanide and subsequent eye baths of potassium iodide solutions and dionin drops.

Pollock (1923) recommended eye lotions containing potassium salts as the iodides, acetates, citrates and chlorides.

Harkness (1925), after reviewing the literature and the opinions of leading American ophthalmologists, reported that there was no specific treatment. He felt that with the various methods of treatment outlined above, the results were not uniform, and there had not been a sufficient number of untreated controls to warrant conclusions. He cited the growing disposition to regard senile cataract as a degenerative process associated with the general health of the individual. The more recent reports in the literature have emphasized the necessity of treating the patient from the standpoint of general metabolism.

Sanders (1925) again called attention to the importance of treating the patient generally as well as locally.

The relation between cataract formation and disturbances of the endocrine organs has been of increasing interest during the past twenty years. The thyroid and parathyroid glands have been the organs chiefly suspected, but the pituitary gland, pancreas, adrenals and ovaries have been cited as organs whose disturbed secretions may result in cataract.

Weeks (1906-7) mentioned a case of Gallan, where cataract occurred in myxedema, and a case of Landsberg (Centralbl. f. prakt. Augenheilk., 1888, S. 39) where cataract developed in association with choroiditis two years after the total extirpation of the thyroid. The case of Wagner (Graefe-Saemisch., Vol. XI, Part 1, p. 331, second edition) was also cited where neuroretinitis of both eyes was observed in a girl of 26 years with myxedema. Thyroidin was given and one eye improved in vision from 20/200 to 20/20, but in the other, in which optic atrophy was noted, there was no improvement in vision. The neuroretinitis was thought to be due to myxedema.

Dunn (1909-10) reported favorable results in the treatment of various eye conditions by the internal administration of thyroid extract. Improvement was noted in cases of cyclitis, interstitial keratitis, sub-acute glaucoma, corneal ulcer and chorioretinitis. Two cases of "rheumatic iritis" were reported, one in a lady of 75 years, who developed rheumatic pains three days after cataract operation, and in whom the pains ceased after thyroid medication. No specific mention, however, was made of the use of thyroid extract in the treatment of senile cataract.

Bennett (1913) reported a cure of recurrent hemorrhages into the vitreous in a young woman with retinitis proliferans after the internal administration of thyroid extract and calcium lactate. Other medication such as calcium lactate alone, mercury inunctions, potassium iodide, iron and tonics internally, and local x-ray treatments were used without results, before the thyroid extract was employed.

Risley (1913-14) reported two young patients who presented ocular conditions which were apparently associated with myxedema. In one case the cornea was vascular and showed a group of isolated gray spots, deeply situated, and in the other case there was a vascular keratitis and recurring superficial ulcers. Both improved greatly in general health and the local conditions showed rapid subsidence.

Lisser (1916) cited the results of treatment of interstitial keratitis by Risley, who found thyroid extract of value in the treatment of such cases. The thyroid was thought to be injured by the general infection, which in turn reduced the nutrition of the eye.

Edmunds (1916) reported the appearance of bilateral cata-

raet in a dog two years after total thyroideectomy. The dog had had convulsions, possibly tetany, following operation. Edmunds cited the case of Westphal who, in 1895, observed a female patient with total thyroideectomy. On the second day after operation tetany developed. In 1900 the patient was again admitted to the hospital in an apathetic state suffering from tetany and "epileptic fits." The symptoms were attributed to the removal of the parathyroid glands. Edmunds also cited the case of Schiller, where operation was performed in 1890 at the age of 36 years for the removal of a large goiter of long standing. Two days after operation tetanic spasms developed, and a few days later albuminuria without casts, edema of the hands, and mental dullness were noted. During the following year, six to eight months after operation, the tetany continued and cataract appeared in both eyes; the right eye was operated upon. The next summer, one year after operation, there was cachexia. The skin was dry, and the hair and nails fell out. A few months later the nephritis became acute and the patient died.

Jeremy (1919) reported post-operative cataracts in a case of goiter in a woman observed in 1914. Three or four months after operation vision began to fail. Both eyes showed opacities, the changes being more marked in one eye. The patient was stout and looked myxedematous, and complained of weakness and frequent tetanic spasms of the legs. Thyroid extract in tablet form relieved the symptoms of tetany, but the myxedema did not improve. The cataracts were attributed to a toxemia uncontrolled because of reduced thyroid and parathyroid secretion.

Dunn (1919) again called attention to the importance of the hypothyroid state in bringing about pathological changes in the eye. No mention, however, is made of the relation between cataract and the thyroid gland.

Szily (1921) pointed out the relation between tetany caused by the absence or dysfunction of the parathyroids and cataract. A number of authors of clinical and experimental reports are cited. Cataracts have been observed following thyroideectomy even when the parathyroids were preserved.

Kirkpatrick (1922) expressed the view that endocrine disturbances were responsible for primary cataract. The removal of the thyroid gland was not considered the sole cause of cata-

ract formation. The possible removal or injury of the parathyroid glands and the compensatory effort of other endocrine glands were considered of more importance in the etiology of cataract.

Zentmayer (1922) brought forth evidence that extirpation of the thyroid gland sometimes resulted in infiltration and ulceration of the cornea with partial blindness. Interstitial keratitis and bilateral cataract was also observed. Many of the convulsive disorders (convulsions of children and eclampsia) were attributed to parathyroid deficiency, and this deficiency was assumed to be an etiological factor in zonular cataract.

Fuchs (1922) stated that zonular cataract was due to hypofunction of the parathyroid glands. The statistics of Hesse were cited, where symptoms of tetany were observed in 81 per cent of all his cases of zonular cataract and in 41 cases of tetany zonular cataract was noted four times. Extirpation of the parathyroids in rats was followed by opacification of the lenses. Tetany in the adult was sometimes associated with the development of soft cataract. The correlation between cataract and parathyroid hypofunction was not clear and there was not enough evidence to show whether there was a direct action of certain chemical substances on the lens or an indirect nutrition disturbance by the intermediary action of the altered ciliary epithelium.

Burden-Cooper (1922) reviewed the subject of etiology of cataract and brought out the importance of the regressive changes in the body as the basis for senile cataract. The association of cataract with diabetes in younger individuals and the frequent occurrences of cataract with tetany was noted.

Hahn (1922) cited the eye conditions, such as falling of brows and lashes, eczematous lid inflammation, deep keratitis, certain types of cataract, uveitis, optic neuritis and retinitis pigmentosa, which are most often associated with hypothyroidism in the literature. This author felt that the variability of reports from thyroid administration in such cases showed that more must be learned about the cause of these conditions before a rational treatment could be instituted.

Schmitt (1922) pointed to endocrine disturbances as etiological factors in the production of uncomplicated cataract, but offered no specific data regarding treatment.

Van Zandt (1923), from his own experience, was relieved of a cataract of ten years' duration following the use of glandular therapy. Several preparations were taken by mouth, but the thyroid substance was probably the only potent one in the mixture.

Ascher (1924) reported therapeutic results in the treatment of cataract in women with ovarian extract. The spontaneous improvement in cases of cortical cataract was pointed out as likely to vitiate any but the most carefully controlled studies.

Hilroishi (1924) reported the results of extirpation of the parathyroid glands. This author found one parathyroid in each lobe of the thyroid in the rat. After their removal a mild course indicated the presence of accessory parathyroids. Half of the animals survived operation. Histological examination, when both parathyroids had been removed, showed that opacity of the lens occurred regularly; when one parathyroid was left opacity was found in only one case (25%). As a rule, the lens turbidity appeared simultaneously in both eyes, between the 7th and the 35th day after operation. There existed radial striae in the axial region, which spread toward the periphery, but did not render the entire lens opaque. This arrest of the process the author attributed to a cessation of the injury and a beginning functioning of the accessory parathyroids. Cataract formation was the most constant finding.

Jackson (1924) urged caution in drawing conclusions from treatment because of the natural tendencies of senile cataracts. He stated that the course of development is usually through many years, and that the process may become arrested or regression may take place, and the vision improve without treatment. This author urged general hygienic care and used no specific medication.

Taylor (1924) employed Dor's method of treatment for senile cataract, using an ointment of calcio-alkaline-iodid, which was less objectionable to use than an eye lotion or bath. Satisfactory results were reported, in early cases, where the treatment was continued without interruption greater than two weeks.

Our first interest was aroused in the medical treatment of senile cataract in 1921, when we (Wm. J. K.) noted the disappearance of opacities in the lens after the use of thyroid extract in the treatment of myxedema.

Upon being called to see a widow of 68 (Case 1) who, within a few days had been operated upon for senile cataract of the right eye, it was observed that there were many signs suggestive of a moderate myxedema. There was intense suffering from the cold. She was constipated. The hair was thin and gray, and the eye-brows were thin. The skin was dry and inelastic, and the nails were longitudinally ridged and brittle. The subcutaneous tissues of the arms proximal to the hands, and the legs proximal to the ankles, were rubbery and myxedematous. There were thick fat pads below the external malleoli and at the junction of the cervical and thoracic spine. The face was somewhat puffy. The systolic blood pressure was 180 mm. (mercury), and the diastolic pressure was 95 mm. (mercury). There were Heberden's nodes on the fingers and there was limited extension and deformity of the left elbow.

A competent ophthalmologist had described opacities in the left lens but did not feel that time for operation had arrived. The vision was definitely reduced, however, and the patient had not been able to read. Because of the symptoms and signs suggestive of myxedema, desiccated thyroid (Armour) one grain (0.065 gm.) twice daily, was started and the dosage was gradually increased until two grains (0.13 gm.) was being taken twice daily. It was impossible, at the time, to carry out any metabolic tests. Within two months the patient stated that the vision in the left eye, which had been greatly impaired, had returned almost to normal. On examination it was found that the opacities of the left lens had disappeared. There was at first some loss of weight associated with a diminution of the myxedematous tissue, and the skin became softer. The thin gray hair was gradually replaced by a very thick coat of dark hair and the eyebrows were restored to a more normal condition. About six months after the desiccated thyroid was begun, pains developed in the clavicles and the scalp became tender. A blood Wassermann, now taken for the first time, was strongly positive. Roentgenograms of the elbow, clavicles and skull showed luetic periostitis. The lesions disappeared under anti-luetic treatment. The vision in the left eye remained unchanged and the general health of the patient was better than for many years. The desiccated thyroid was continued in small doses. There was no history of known luetic infection although the

husband had died suddenly many years before, at about fifty years of age, presumably from an aneurism.

In 1925, four years after the desiccated thyroid was begun, the vision in the left eye was practically normal and the lens showed only slight opacities at the periphery. Late in 1925 death occurred from an intercurrent infection. At autopsy the clavicle showed the healed luetic lesion. No other evidence of lues was noted. *The thyroid gland was small and practically replaced by fibrous tissue.*

Although in this case the cataracts were considered to be of the senile type, it is likely that lues was a factor in their production. The observations of the changes in the lens were incidental and incomplete for comparative studies. The lighting up of the periosteal luetic lesions after the use of thyroid extract was of interest.

The results with the first case appeared unusual, but we did not begin to make a more thorough study of senile cataracts and other eye conditions until another similar experience occurred. In 1923, the second patient (Case 2), female, age 60, came for examination, complaining of failing vision for eight years. An examination, by a competent ophthalmologist, revealed bilateral cataracts and corneal scarring. During the last two years the vision had failed rapidly and she had to give up work because of inability to get about alone. Only the largest newspaper type could be read. She could read better in a dim light. The physical examination showed a dry skin; the hair was gray, thin and dry, and the eyebrows thin on the outer half; cilia absent; nails thin, brittle, with longitudinal ridges. The axillary and pubic hair were very thin. Fat pads were marked at the junction of the cervical and thoracic spine and below the external malleoli. The subcutaneous tissues were of the myxedematous type. The blood counts, urine and stool were normal. A blood Wassermann was negative. The basal metabolic rate was not observed.

The treatment instituted was Armour's desiccated thyroid, one grain (0.065 gm.) a day for the first week; three grains (0.195 gm.) a day during the second week, and four grains (0.26 gm.) a day during the third and fourth weeks. On four grains a day there was slight evidence of toxicity. Later the

dosage was increased to six grains (0.4 gm.) a day without toxic symptoms.

There was definite improvement in vision within three months. Medium sized newspaper type could be read. There was less difficulty in getting about the street, and work had been resumed. Within four months the vision in one eye was said, by the patient, to be almost normal and the other eye had shown further improvement. The corneal scars were less marked. No accurate observations were made of the opacities at this time. The hair was getting darker and thicker and the eyebrows were returning to the normal condition. The cilia were practically normal. There had been at first a loss of weight but during the four months the loss had been regained. The subcutaneous tissues appeared more normal. There had been transient pains in the eyes during treatment.

One year after treatment was begun, the patient reported for examination upon request. She had not reported because she felt so well and had been working regularly. The vision had remained about the same as at the last examination. There was further improvement in the general condition. The desiccated thyroid had been continued with four grains (0.26 gm.) a day without toxic symptoms. An examination by a competent ophthalmologist showed opacities in the lens and some scarring of the cornea of both eyes. Exact figures for visual acuity before and after treatment were not obtainable, although there can be no doubt that there was improvement in the vision. It was also difficult to state whether the improved vision came from the clearing of the corneal scars or from the reduction of the opacities in the lens.

These isolated observations caused some inquiry into the literature. We found evidence, as stated above, of a possible relationship to disturbances of the parathyroid or thyroid glands. Also there was the frequent reference to the beneficial results from the use of iodine and its compounds. Whether the action of iodine compounds and desiccated thyroid is the same, is, of course, open to speculation.

We decided to combine the facilities of the Out-Patient Departments of Medicine and Ophthalmology in studying a group of cases of senile cataract. In most cases a careful history and physical examination were obtained. Routine urine examina-

tions, blood counts, blood Wassermann tests, chemical tests of the blood for non-protein and urea nitrogen, uric acid and creatinine and the basal metabolic rate were obtained. Later the blood chemistry studies and basal metabolic rates were not made as all were found to be within normal limits. The blood Wassermann tests were all negative. The physical examination in practically all cases showed the changes, with some variations, as described above.

The visual acuity tests were made under the ordinary lighting conditions of office and clinic and were subject to slight variations. The charts were always illuminated by the same degree of artificial light but the patients were in ordinary daylight. The observations were made at about the same time of day. The readings were taken under the most favorable conditions as to correction with glasses; that is, they were taken with their correction if the cataracts were not so advanced as to make all lenses useless.

No case was considered improved unless the patient could read a smaller line on the chart, although it is possible that this is within the limit of error.

Treatment was carried on by the use of Armour's desiccated thyroid alone, unless there were contraindications for the use of thyroid medication. The dosage was begun with one or two grains a day and gradually increased until toxic symptoms were produced in a few cases. Some patients required six to eight grains a day before showing toxic symptoms. In some instances toxic symptoms were produced without causing any changes in vision. Improvement in general health was noted in many cases in which the vision was not improved as well as in those cases in which vision was definitely improved.

There were many problems connected with the treatment of patients with cataract in the clinic. Most of them were below par mentally and co-operation could not be assured. Some patients came from a distance and it was not deemed wise to allow them to continue thyroid medication without proper supervision. A number of patients had incomplete records because of failure to return for observation. In these instances it is not known whether they were improved and for this reason failed to report, or whether they had become worse, as they could not be located. Other cases were excluded from the study because

of incomplete examinations of the eye. A third of our cases, covered by this report, were examined in the private office of Dr. W. S. Franklin, who has kindly consented to our use of his data. In some of these cases complete general histories and

TABLE I

Name	Age	Sex	Vision at Beginning		Vision Now		No. of Mo.	Dosage Grains	W
			V. R. E.	V. L. E.	V. R. E.	V. L. E.			
C. T.	57	F	20/40	20/70	20/70	20/70	26	2-3	
E. S. 68991	74	F	Lt. percept.	20/40	Lt. percept.	20/50	6	2-3	
E. Sc. 107905	74	M	Fingers 5 ft.	20/100	Movement hand	20/100 Operated	6	1	
F. Mc. 109824	54	M	20/50	20/200	20/40	Lt. percept.	9	3	
O. D.	57	M	Fingers 8 ft.	Fingers 4 ft.	Lt. percept.	Lt. percept.	3	6	
St.	34	M	20/50	Fingers 10 ft.	Operated		6	3-6	
Ch.	40	F	20/40	20/40	20/70	20/70	23	3	
L.	58	F	20/200	20/70	Operated		6	3	
F. P.	69	F	Lt. percept.	20/30-2	Lt. percept.	20/30	17	2-3	S
S. Mc. 100418	61	F	20/70	Lt. percept.	20/70	Lt. percept.	8	3-4	S
M. De. 68152	54	F	20/70	20/70	20/70	20/70	7	3	S
S. 101629	60	F	20/20	20/30	20/20	20/30	13	1-4	S
J. C. 83079	75	M	Fingers 5 ft.	Fingers 5 ft.	Fingers 5 ft.	Fingers 10 ft.	30	1-3	S
M. St. 110029	58	F	20/20	20/40	20/20	20/40	28	1-3	S
P. R. 125839	63	F	20/70	20/50	20/70	20/50	7	1	S
M. F. 85419	65	F	20/30	20/20	20/30	20/20	13	1-3	S
Fr.	58	F	20/30	20/40	20/30	20/40	9	3	S
P.	57	M	20/40	20/40	20/40	20/40	3	3-5	S
H. T. 106929	65	F	20/40	20/200	20/30	20/70	3	2-3	I
F. G. 107843	66	F	Lt. percept.	20/70	Lt. percept.	20/50	10	3	I
M. S. 59762	57	F	20/40-2	20/40-2	20/30	20/30	23	3	I
J. P.	38	M	20/40	20/20	20/20	20/20	33	1-6	I
C. B.	82	M	20/70	Lt. percept.	20/40	Lt. percept.	11	1-3	I
W. L.	77	M	Fingers 5 ft.	20/70	20/200	20/40	6	1-4	I
C. M.	74	M	20/200	20/40	20/70	20/30	1	1-2	I
W.	55	F	20/20	20/200	20/20	20/100	9	3	I
C.	56	F	20/100	Amaurosis	20/70	Amaurosis	7	3	I
F.	67	M	20/30	20/40	20/20	20/20	23	2	I

Worse (W)—28.8%; Same (S)—35.6%; Improved (I)—35.6%.

physical examinations were not obtained, because of the reluctance of these patients to undergo such examinations. The condition of the circulatory system and the thyroid gland was, however, noted in these few instances.

Our small series of twenty-eight cases does not lend itself to a statistical study either as to type of cataract or as to the stage of the process. Table 1 shows the age, sex, comparative tests of visual acuity before and after treatment, the duration of treatment, and dosage of desiccated thyroid.

In the twenty-eight cases, ten, or 35.6 per cent, showed improvement; ten, or 35.6 per cent, were unchanged, and eight, or 28.8 per cent, became worse under treatment.

Two cases are worthy of special mention. One of these, not included in our table, was in a male of 47 years, seen first in November, 1923; he had had a bilateral cataract, with impaired vision in the left eye for five years and in the right eye for two years. At the time of examination the vision in the right eye was limited to light perception and the capsule of the lens had been needled twice during March, 1923, seven months before. There was incipient cataract in the left eye with 0.1 of normal vision. Glasses did not improve either eye. Examination revealed the lenticular material hanging in thick, white clouds in the eye upon which the needling had been done. The general and laboratory examinations were negative except for a trace of sugar in the urine, but the fasting blood sugar was only 0.082 per cent. Desiccated thyroid one grain (0.065 gm.) was begun three times a day. The patient did not return for six weeks and when he noted improvement the dose had been doubled. The clouds of lenticular material were practically entirely absorbed except for a few fibrous looking strands which projected from the periphery into the center where the lens had been. Two months later it was even clearer, and it was found that with a cataract glass he was able to read the 0.7 line with ease, and with a reading correction was able to read ordinary print. This striking result was attributed to the thyroid gland treatment, although the result may have been a coincident.

The other case of special interest was that of a widow, age 60, who was first seen in October, 1923, because of failing vision in the left eye. The vision was 0.5 in this eye and early opacities in the lens were noted. The general examination revealed the

signs frequently associated with old age. The heart was enlarged and there were presystolic and systolic murmurs at the apex, indicating mitral stenosis and insufficiency. The mitral valve lesion was probably based on attacks of chorea in childhood. No enlargement of the thyroid was observed. On thyroid medication, 1 grain (0.065 gm.) three times a day for two weeks and four times a day for the next two weeks, the opacities in the left lens entirely disappeared. The medication was continued for a fourth week, when an attack of auricular fibrillation developed. The medication was stopped. *Five months* later there was a definite enlargement of the thyroid gland with nodular areas and toxic symptoms were noted. At operation adenomata were removed. Since operation there has been no return of toxic symptoms. The attacks of auricular fibrillation have ceased. The opacities were not found at the time of the last examination.

In this case it is difficult to state which of the conditions was responsible for the auricular fibrillation. There was no doubt of the presence of mitral valve disease with moderate stenosis. In such cases auricular fibrillation is relatively common. The toxic adenomatous goiter, which was not noted at the first examination, rapidly increased in size or was made obvious by the loss of subcutaneous tissue about the neck, could easily have been the exciting cause for the attacks. The basal metabolic rate was normal before beginning treatment. Either of the above conditions should make one cautious in the therapeutic use of thyroid gland products.

#### DISCUSSION

In presenting this small series of cases, we are convinced that the thyroid gland preparation used improved the general health of the patient in most instances. Whether the improvement noted in vision, and the disappearance of the opacities is the result of the specific action of the thyroid substance administered or merely the result of improvement of the general condition, indirectly influencing the eye, we are unable to state. We feel that senile cataracts represent the local changes in the lens of individuals who are the subjects of general degenerative disturbances. This is strongly suggested by their appearance late in life, their bilateral occurrence and the tendency to vary

with the general health of the patient. While opacities may remain stationary for years, or may even clear up without treatment, thereby making it difficult to prove the value of any therapeutic procedure, we feel that these very facts should encourage us to renew our efforts along more general lines of investigation. Such studies must be made on a large series of cases, with ample untreated control and the types of cataracts must be clearly differentiated.

From our studies, we are unable to state that any particular type of cataract responded better to treatment than another. We were dealing, for the most part, with advanced cases, in which we could not expect much improvement. The incipient cases offer better hope of cure. The responsibility for initiating future investigations rests with the ophthalmologists, who may discover peripheral changes in the lens before there is any definite reduction in the visual acuity. These changes in the lens are noted when refraction is done. A warning, however, should be sounded for the ophthalmologist who may enthusiastically begin the administration of thyroid substance or other drugs without having full knowledge of the general condition of the patient. Here is an opportunity for close co-operation between the ophthalmologist, who may see the patient first, and the internist who is better able to decide when general treatment should be instituted and to follow the patient through the period of administration.

The use of iodine or its compounds in the past, both locally and generally, has been shown to be of value in the treatment of senile cataract. The action of the iodine is not as yet clearly understood. It is supposed to have an action in removing fibrous tissue generally. The action may be through an activation of the thyroid gland and the action of the iodides and thyroid substance may be the same. The general circulation may be improved by these substances and in this way the local circulation and nourishment of the eye may be stimulated. Such therapeutic agents as radium, x-ray, mercury cyanide and others may also increase the local circulation and metabolism of the eye to bring about improvement.

We feel that one may expect better results in early senile cataract if the iodides are used locally in the eye and thyroid substances or the iodides are given internally. Further studies

are needed on the metabolism of sodium, potassium, magnesium and calcium in relation to the changes in the lens in senile cataract. The work of Burge (1918), who showed that in the cataractous lens the potash is reduced to 9.8 per cent from the normal of 38 per cent, and the calcium is increased from a negligible quantity of 0.08 per cent to 15 per cent, is of interest. The increase of magnesium was found to be less marked, but definite.

When the metabolism of cholesterol is better understood we may find a relationship between it and the formation of cataract in the senile as well as in the diabetic patient.

The frequent occurrence of tetany, with disturbed calcium balance, parathyroid or thyroid disease and cataract formation, indicates a definite relationship. The endocrinologist should co-operate in this field of investigation.

There is no great danger in the administration of thyroid substance, if the patients are carefully studied before treatment and watched for toxic symptoms. Improvement was noted in most of the cases benefited before any toxic symptoms appeared. The basal metabolic rate was within normal limits in practically every case, and in a few was toward the lower limit of normal. We do not feel that a normal metabolic rate contraindicates the use of thyroid medication, if it is carefully supervised. We have been using small doses of thyroid substance, for many years, as a general tonic, and have been pleased with its beneficial effects. In this we have felt that the action of the drug was probably similar to that obtained with small doses of the iodides.

We have employed thyroxin in a few cases of advanced senile cataract, but the results have not, thus far, been striking. Parathyroid hormone is being tried, under the direction of Dr. H. Lisser, and may be the subject of separate report.

Other eye conditions have been treated with thyroid substance. In some cases of corneal ulcer, intractable to ordinary methods of treatment, the improvement has been prompt and striking. In glaucoma we have not had the opportunity to study the cases long enough to determine the possibility of improvement.

We wish to thank Dr. W. S. Franklin, Clinical Professor of Ophthalmology, for his co-operation and suggestions.

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## THE EFFECT OF THYROID DEFICIENCY

On Chart 1A the growth of the hypophysis in the male rats is compared with that of the body in weight after thyroid removal at the stated ages. It is evident that the reaction of the gland to thyroid deficiency is quite different from that of the body as a whole. An acceleration instead of a retardation of growth has been induced. No evidence of a pubertal influence is noted.

From Table 1 it is seen that the weight of the hypophysis of the male tests is greater than that of their controls. This is evidence of an absolute hypertrophy.

On Chart 1B the growth of the hypophysis in the female rats is compared with that of the body in weight after thyroid removal at the stated ages. It is evident that the organ is not retarded to anywhere nearly the same degree as is the body as a whole. Acceleration of growth follows thyroid removal at 65 days of age. This is indication that puberty is a factor in determining the reaction in the female. Although there is a hint that the period of pubertal adjustment determines a tendency to parallelism of the hypophysis with the body weight in the direction of change in degree with the change in age at time of thyroid removal, yet here as in the male the general picture indicates that the response of the gland is distinct in type as well as in degree from that of the body.

From Table 1 it is seen that absolute hypophyseal hypertrophy only occurs in the female when the thyroid is removed at 65 days of age.

The data justify the conclusion that the growth of the hypophysis is specifically influenced by thyroid deficiency.

From this the natural deduction would be that there is a specific thyroid-hypophysis incretory relationship. There are certain facts which seem inconsistent with this deduction.

A biometrical analysis of the weight interrelations of the glands of internal secretion has been made by the method of partial correlation (5) from the values furnished by the organ weights of 121 of the male and 121 of the female rats which served as controls in the thyroid studies. This use of the same material for the two types of investigation enhances the validity of the interpretations.

TABLE I  
THE OBSERVED MEAN WEIGHT OF THE HYPOPHYSIS (IN GRAMS) OF THE SEVERAL GROUPS OF RATS  
"Beginning" values for "Control" and "Test" groups computed according to method referred to in the text.

Age Series	THYROPARATHYROIDECTOMIZED						PARATHYROIDECTOMIZED					
	At Beginning			At End (150 days)			At Beginning			At End (150 days)		
	Ref.	Contl.	Test	Control	Test	Control	Contl.	Test	Control	Contl.	Test	
MALES												
23	0.0017±0.0001	0.0018	0.0017	0.0083±0.0002	0.0008±0.0005	0.0017	0.0017	0.0081±0.0002	0.0064±0.0001	0.0064±0.0001	0.0064±0.0001	0.0064±0.0001
30	0.0023±0.0001	0.0022	0.0022	0.0082±0.0003	0.0033±0.0003	0.0023	0.0023	0.0088±0.0002	0.0063±0.0001	0.0063±0.0001	0.0063±0.0001	0.0063±0.0001
50	0.0034±0.0001	0.0033	0.0033	0.0081±0.0003	0.0097±0.0005	0.0033	0.0033	0.0070±0.0002	0.0063±0.0001	0.0063±0.0001	0.0063±0.0001	0.0063±0.0001
65	0.0045±0.0001	0.0043	0.0043	0.0080±0.0002	0.0030±0.0003	0.0014	0.0014	0.0087±0.0001	0.0066±0.0002	0.0066±0.0002	0.0066±0.0002	0.0066±0.0002
75	0.0010±0.0001	0.0017	0.0018	0.0084±0.0003	0.0056±0.0003	0.0018	0.0017	0.0078±0.0002	0.0057±0.0002	0.0057±0.0002	0.0057±0.0002	0.0057±0.0002
100	0.0050±0.0002	0.0058	0.0058	0.0072±0.0001	0.0082±0.0003	0.0058	0.0057	0.0072±0.0001	0.0063±0.0002	0.0063±0.0002	0.0063±0.0002	0.0063±0.0002
FEMALES												
23	0.0020±0.0001	0.0019	0.0019	0.0109±0.0002	0.0106±0.0002	0.0020	0.0020	0.0108±0.0003	0.0052±0.0003	0.0052±0.0003	0.0052±0.0003	0.0052±0.0003
30	0.0024±0.0001	0.0023	0.0023	0.0103±0.0006	0.0110±0.0003	0.0024	0.0023	0.0110±0.0004	0.0052±0.0003	0.0052±0.0003	0.0052±0.0003	0.0052±0.0003
50	0.0040±0.0001	0.0038	0.0038	0.0107±0.0004	0.0092±0.0005	0.0010	0.0039	0.0104±0.0003	0.0054±0.0003	0.0054±0.0003	0.0054±0.0003	0.0054±0.0003
65	0.0052±0.0003	0.0051	0.0049	0.0093±0.0003	0.0112±0.0004	0.0051	0.0050	0.0100±0.0003	0.0055±0.0005	0.0055±0.0005	0.0055±0.0005	0.0055±0.0005
75	0.0057±0.0002	0.0055	0.0055	0.0103±0.0003	0.0102±0.0005	0.0054	0.0054	0.0104±0.0004	0.0060±0.0004	0.0060±0.0004	0.0060±0.0004	0.0060±0.0004
100	0.0072±0.0002	0.0070	0.0070	0.0104±0.0004	0.0091±0.0003	0.0070	0.0069	0.0104±0.0004	0.0063±0.0003	0.0063±0.0003	0.0063±0.0003	0.0063±0.0003

TABLE II

THE ABSOLUTE AND THE RELATIVE PERCENTAGE RATE OF GROWTH OF  
THE HYPOPHYSIS OF THE SEVERAL GROUPS  
THYRO-PARATHYROIDECTOMIZED GROUPS  
PARATHYROIDECTOMIZED GROUPS

	MALE			FEMALE			
	Thyro-parathyroidectomized Groups						
Age Series	Control-%	Test-%	T/C	Control-%	Test-%	T/C	CM*/CF*
23	366.3	466.5	127.3	473.7	457.9	96.7	77.3
30	272.7	322.7	118.3	367.5	380.4	103.5	74.2
50	145.5	193.9	133.3	181.6	142.1	78.3	80.1
65	86.1	109.3	127.0	92.2	128.6	139.5	93.4
75	78.7	100.0	127.0	87.3	85.5	97.9	90.1
100	24.1	41.4	171.4	48.6	30.0	61.8	49.6
	Parathyroidectomized Groups						
23	368.2	281.0	76.3	440.0	310.0	70.5	83.7
30	282.6	187.0	66.2	368.1	298.3	81.0	76.8
50	139.4	90.9	65.2	160.0	115.4	72.1	87.1
65	97.7	50.0	51.2	96.1	82.0	85.3	101.7
75	62.5	21.3	34.0	75.9	42.6	56.1	82.3
100	24.1	10.5	43.6	48.6	20.3	41.8	49.6

\* C.M., control male; C.F., control female.

A study of the distribution of the thyroid weight values showed that these were divisible into two groups (6), a group of normal (or usual range) and a group of heavy thyroids. On the basis of the analysis of the correlation between the first group and their respective body weights and the second group and their respective body weights, the conclusion was drawn that the first group represented thyroids of normal (or usual) range of activity, and the second represented thyroids of enhanced activity. The biometrical analysis of the weight interrelations of the endocrine organs was therefore similarly classified.

It was found that within the usual range of thyroid size there is no valid degree of weight association between hypophysis and thyroid in the adult rat (150 days of age) when the general factors for organ size carried by the body weight

and the assumed influences for organ size exerted by the other secretory organs are held constant by appropriate statistical treatment. The fifth order correlation coefficient in the male is 0.042, and in the female 0.127.

Although there is a valid positive association between the two glands when the general factors of influence are in force, this is largely due to the body size factor, since when this is held constant by the method of partial correlation the zero order coefficients of  $0.371 \pm 0.062$  for the male and  $0.299 \pm 0.067$  for the female drop to 0.112 and 0.129, respectively. Consistent with this dependency of the thyroid-hypophysis association on the body size, is the fact that the correlation between hypophysis and body weight is high and positive, being  $0.701 \pm 0.031$  in the male and  $0.515 \pm 0.045$  in the female.

These results are apparently at variance with the idea of a specific secretory relation between thyroid and hypophysis, since they show definitely that within the normal (usual) range of thyroid size and presumably activity the shifts therein are not productive of shifts in weight of the hypophysis, which are independent of shifts in body weight. That is to say the shift in hypophysis weight which occurs with shift in thyroid weight (activity) is not due in this group to a specific relation between thyroid and hypophysis, but is due to the relation of the hypophysis to the effectiveness of the general body factors as related to thyroid activity (weight).

Now, not only does complete thyroid deficiency bring out a specificity of reaction on the part of the hypophysis, which is not exhibited under usual conditions, but a like phenomenon is exhibited when thyroid activity is above the usual.

While the literature, summarized by Cameron and Carmichael (7), gives evidence of pituitary hypertrophy on thyroid feeding, more definite information in this direction is had from the pertinent weight correlation coefficients derived from the heavier than usual thyroid weights of my control rats. These show that there is a high degree of positive correlation between the heavier or more active than normal thyroid and the hypophysis which is independent of the general factors for size carried by the body weight. The first order coefficient obtained when body weight is held constant is 0.452 in the male, and 0.653 in the female, as against the zero order values of  $0.117 \pm 0.112$ .

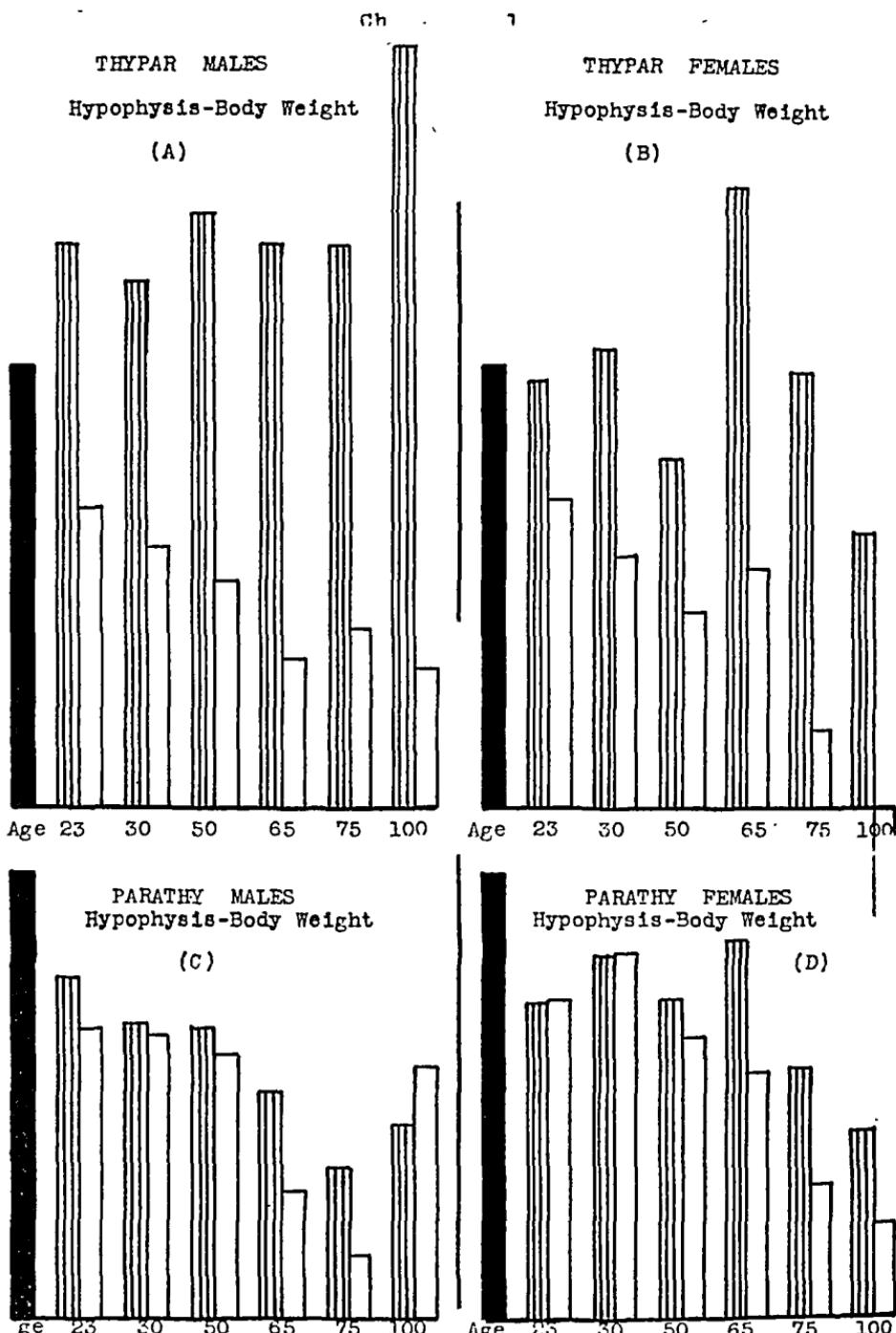


Chart 1. The growth of the hypophysis compared with that of the body in weight. A—Thyro-parathyroidectomized males. B—Thyro-parathyroidectomized females. C—Parathyroidectomized males. D—Parathyroidectomized females. Order of sequence given by the superscript.

and  $0.399 \pm 0.092$  for the two sexes, respectively. Further stabilization for the influences assumed to be exerted by the other incretory organs does not alter significantly the first order values.

The conclusion is that there is a specific weight association between the hypophysis and the mildly overweight thyroid. The natural deduction from this would also be that there is a specific incretory relation between hypophysis and overweight thyroid.

Indirect evidence in support of the general conclusion is had from the fact that the growth response of the hypophysis to the condition of essential undernutrition induced by parathyroid removal (4) is the same in type as that of the body as a whole (Chart 1C and D), and similar to that reported in conditions of undernutrition produced by dietary deficiency (8) (namely a retardation of growth), whereas its response when the same fundamental state of undernutrition is produced by thyroid deficiency is an hypertrophy or virtual independence of the general body response. This indicates the presence in this case of a dominating factor which is not present in the others, the nature of which can be no other than a specific thyroid-hypophysis incretory relationship.

From these data it is evident that the size of the hypophysis is related to thyroid activity only when this passes the limits assumed to be normal in either direction. The lack of weight correlation within the usual range of thyroid size leads to the inference that there is no incretory interrelationship under these conditions. The objection might be raised that expression of weight association between the two glands is prevented by an arithmetical balancing of the results (tendency to hypophyseal enlargement) of the extremes of thyroid activity, were it not for the fact that a positive weight association exists which is dependent on body size. Such being the case it is probable that the lack of specific weight correlation within the usual range of thyroid size and activity is due to the fact that the hypophysis, like the other organs, is dependent on the effectiveness of the total growth of the body, in which the thyroid plays no specific rôle aside from its part in the regulation of the metabolic level (4). Under normal conditions it might well be that no expression would be given of any specific hypo-

physis-thyroid incretory relation in so far as size association is concerned. Indeed it may be that no incretory relation is in force under usual conditions, and that this only comes into play in conditions of organic imbalance when thyroid activity passes the normal limits in either direction. In other words, it is probable that the specific dependency of the hypophysis is potential or dominant under usual conditions of thyroid activity, and only comes into action to be expressed as an enlargement and possibly an enhancement in function when thyroid activity exceeds the usual limits.

The actual functional significance of the specific incretory association between thyroid and hypophysis is unknown. Since conjectural interpretation is at all times permissible, I will outline what to my mind appears to be the most probable basis of the relationship from the data at hand. This is done with the decided understanding that the matter at the present time is solely in the speculative stage, that the opinions expressed are purely tentative, and that their sole utility is to serve as a foundation for further work leading to ultimate clarification.

The studies of Kojima (9), Smith and Smith (10), Loeb and Kaplan (11), Flower and Evans (12) and others show pretty definitely that the anterior lobe of the hypophysis is the part of the organ which is concerned in the thyroid-hypophysis incretory association. The cumulative experience of many investigators has established the fact that a function of the anterior lobe of the hypophysis is concerned in growth. This work beginning with Cushing (13) and continuing with Robertson (14) down to the recent startling results of Evans (15) and his collaborators is too well known to need extensive citation.

The problem is thus narrowed down to a consideration of the respective rôles of the thyroid and the anterior lobe of the hypophysis in growth. The reader will note that I write of the "respective" and not of the "replacement" rôles of the two organs in this phase of physiological activity. This is because the work of Smith and Cheney (16) and others as discussed in earlier papers (1) (2) has effectually disposed of the idea that the hypophysis functions vicariously for the thyroid when this is lacking. The fact that there is no correlation between growth retardation in body weight and growth reaction of the hypophysis to thyroid removal at the different ages (shown in Chart

1A and B) is consistent with the idea of the inadequacy of the once-held opinion.

In the paper which dealt with the interpretation of the rôle of the thyroid in growth (4) it was pointed out that there are two types of growth: e. g., growth by increase in cell mass and growth by increase in cell number. It was also pointed out that since growth is a process of energy utilization, it is capable of being expressed in terms of intensity and capacity factors. The analysis of the data led to the conclusion that the rôle of the thyroid in growth is that of a determinant of the capacity factor, that the intensity factor is largely regulated by catalysts other than those produced by the thyroid, and that the thyroid is more largely concerned in growth by increase in cell mass than in growth by increase in cell number. A comparison of body growth in weight and length (17) and the study of the growth of the reproductive system of the same thyroidless (18) animals substantiate the interpretation.

Now it is obvious that while it is convenient and even necessary for purposes of analysis to subdivide the phenomenon of growth into its various aspects, all the several phases are interdependent and no strict mathematical delimitation is possible. It is only the question of more and less, not of how much, that can be answered at the present time.

It can be assumed that the hypophysis is concerned either in growth by increase in cell number or in the intensity factor of growth or in both.

Supporting the first conception is the skeletal overgrowth of acromegaly, a condition associated with hyperfunction of the anterior lobe of the hypophysis. Consistent with the second is the adiposity of hypofunction of this part of the gland in man. For a diminution in the intensity factor of growth, with thyroid function persisting, might well result in a relative increase in the capacity factor which would be expressed in a relatively greater than normal growth by increase in cell mass.

The results of the administration of anterior lobe extract to thyroidless rats by Flower and Evans (12) led them to imply that thyroid deficiency conditions an underfunctioning of the hypophysis. This conclusion, I believe, will eventually be modified.

Chart 1A and B shows that the hypophysis of the thyroidless rats of both sexes is larger per unit body weight than that of the controls. In all groups of males the organ is even absolutely heavier in the tests than in the controls, notwithstanding the lesser body weight, and in 66 per cent of the groups of females it is either the same or heavier in the tests than in the controls.

It may well be that the absolute functional capacity of the hypophysis in the 30 and 100-day-old series of the females is less than normal, indeed it may be that the hypertrophied organ is less functionally active per unit body weight. All experience with physiological and non-pathological enlarged organs speaks against such a view. Yet reasoning by analogy is no proof, nor can proof be given at the present time by measurement of output. Therefore if Flower and Evans choose to stand by their guns it will be difficult to dislodge them on a basis of direct observation. It is possible, however, to bring forward an alternative hypothesis which is consistent with the valid observational data at hand. But before going on to this let us see whether or not my results are consistent with the assumption that the hypophysis is concerned in growth by increase in cell number and in the intensity factor of bodily increments.

As the animal grows older, growth by increase in cell number is a decreasing proportion of total growth, and growth by increase in cell size (mass) is an increasing proportion. Hence on the assumption that the hypophysis is directly concerned in the former the part played by the organ in growth decreases with age by virtue of the natural limitations of the organism, while that of the thyroid increases by virtue of its being a large determinant in growth by increase in cell size. Therefore thyroid removal at progressive stages of development would deprive the organism of a stimulus of relatively increasing importance for growth, while at the same time the capacity for response of the body to the hypophyseal stimulus is decreasing. The result would naturally be an increase in growth retardation with increase in age at time of thyroid removal. If on the other hand thyroid deficiency conditions an underfunctioning of the hypophysis with respect to growth, it would be expected that the effect of this on growth would be most marked at the

age of maximum intensity, or in the younger animals, with a consequent greater or equal retardation in the younger than in the older age series. If this does not happen it would be expected that the effect of the hypophyseal stimulus to growth by increase in cell number would be greatest at the earlier ages, and that this would be expressed by a lesser retardation in the rats thyroidectomized at the younger than at the older ages, when the ability to respond to the stimulus is reduced. Since this is what occurs, observation is consistent with assumption. Such consistency, however, is not proof.

The assumption that the intensity factor of growth is largely determined by the hypophysis in the thyroidless rats is supported by the growth capacity curves for body weight of these animals (4). It was pointed out in their analysis that the values fall below the normal immediately after thyroid removal, but soon recover and follow the normal course with age, both in degree and type. That is to say the intensity factor as represented by grams increment per unit mass per unit time is normal for the age. If the above assumption is correct this is what would be expected. The first effect of the lowered metabolic level consequent upon thyroid removal would be a lowering of the level of functional activity of the hypophysis as well as of the rest of the body. The value of the intensity of growth would then fall below the normal. The specific secretory relation of the thyroid to the hypophysis exhibited in conditions of thyroid dysfunction produces an hypertrophy or inhibition of growth retardation of the latter with the result that its activity is greater than normal per unit mass of body tissue. Then and if the hypophysis is concerned in the intensity factor of growth, the relative increase in growth stimulus given by the hypophysis would tend to counterbalance the general decrease in the ability to respond, due to the lowered metabolic rate and the intensity factor would be brought back towards the normal level. Fact is seen to be consistent with assumption. The correctness of the latter is, however, not to be established by these observations alone. They are merely suggestive indices pointing the way to ultimate solution.

The validity of the assumption should not be attacked on the basis of the fact that a like tendency of adjustment of the intensity level of growth to the norm occurs in the parathyroidless

groups. Here the thyroid is active along with the hypophysis. Although the intensity factor is undoubtedly regulated by catalysts other than those produced by the thyroid, when these are absent, it is by no means to be considered that this is uninfluenced by them when present. Nor must the idea be had that the thyroid is the sole regulator of the capacity factor of growth. It certainly is not the only determinant of the metabolic level, for metabolism and growth in mass proceed after the thyroid has been removed. The two phases of growth are interrelated and interdependent. This does not preclude their separation in analysis, nor destroy the validity of the argument that the one is regulated by a different set of catalysts than the other. The facts show that the thyroid is a major determinant of the value of the capacity factor (4). Inference leads to the idea that the hypophysis is the chief regulator of the intensity factor. Whether this will be established as fact remains to be seen.

Now Flower and Evans (12) report that normal growth of thyroidless rats is preserved when these are treated with anterior hypophyseal extract. They suggest that the growth dystrophies of thyroid deficiency may be referable to anterior hypophyseal underfunctioning resulting from the thyroid lack, and that the growth resumption which obtains on thyroid therapy is due to the reestablishment of normal hypophyseal function. An alternative explanation of their results is as follows:

Due to the interdependency of the intensity and capacity factors of growth it is obvious that a positive stimulation of one would, other things being equal, produce a positive change in the expression of the activity of the other. A negative stimulation of the one would similarly produce a negative change in the expression of the other. This is what occurs immediately after thyroid removal. Soon, however, the intensity factor recovers and becomes the value characteristic of the age, notwithstanding the fact that the capacity factor is still below the normal level. Since the only other organ of known specific importance to growth is the anterior lobe of the hypophysis, and since the hypophysis hypertrophies after thyroid removal, thus indicating increased functional activity per unit body mass, the natural assumption to be made is that a function of the anterior lobe of the hypophysis is largely concerned in the regulation of the intensity factor of growth.

Granting the assumption, the administration of anterior hypophyseal extract to thyroidless or even to normal rats would result in an absolute increase in the stimulus to the intensity factor. This in turn would result in a raising of the absolute level of the capacity factor, the extent of which would depend on the amount and efficacy of the administered stimulus, and the expression of which would be an increased growth in body weight. Thyroidless animals could well be brought to the normal growth level by such a procedure. My thyroidless rats did not reach normal growth in mass (grams per day) because the intensity factor was not artificially stimulated by the administration of anterior hypophyseal extract. The detailed exposition of the process of recovery of the intensity factor is given in an earlier paper (4) and need not be repeated.

It is thus evident that the conception of Flower and Evans (12) is unnecessary and not in accord with the data as a whole.

The resumption of growth in thyroidless rats to which thyroid preparations are given is not due to an increase in anterior hypophyseal function. It is an expression of the fact that such treatment raises the metabolic level, raises the ability of the tissues as a whole to work over more materials, raises the level of the materials available for growth, and raises the rate at which these are incorporated into the body. That is to say, the capacity factor is brought back towards its normal level and growth as expressed by grams increment per day is enhanced. The introduction of the hypophysis into the picture as a dominant factor is unnecessary.

Turning now to consideration of the response of the hypophysis to thyroid deficiency in the female it is seen from Chart 1B that there is a tendency for the direction of change in degree with change in age at time of thyroid removal to be the same as that exhibited by the body weight from puberty (65 day old series) onward.

From the discussion of the preceding paper (18) this phenomenon is taken as indicating a dependence of the response on the effectiveness of the general growth processes of the body, and a virtual independence of the organ from the thyroid in any specific sense.

At first sight, then, this response of the hypophysis of the female would seem to be inconsistent with the general principle

Chart

2

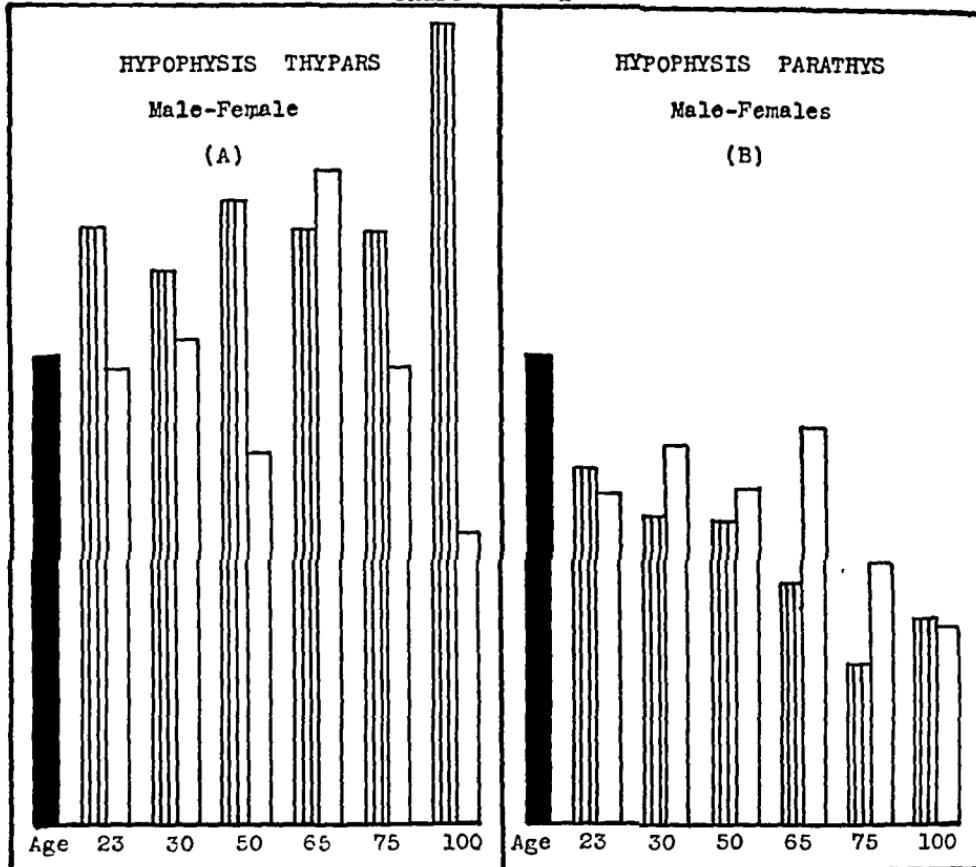


Chart 2. The growth of the hypophysis in the male compared with that in the female after A—Thyroid removal, and B—Parathyroid removal at the stated ages. Order of sequence given by the superscript.

if the idea of a specificity of relationship with the thyroid is valid. Such an apparent paradox demands clarification. Fortunately the necessary data are available.

The age of 65 days is the approximate time of first appearance of corpora lutea in the ovaries of the Wistar albino rats (19). This is obviously the period of the first surge in secretory activity of the ovary. From Chart 1B it is seen that the coming into play of this new factor is accompanied by a marked change in the response of the hypophysis to thyroid removal. Not only does the course of change with age tend to parallel that of the body in weight, but it is at this time alone that thyroid removal is followed by hypertrophy of the hypophysis.

The natural conclusion is that these shifts are conditioned by the secretory activity of the ovary. Such a conclusion is

justified not only by the immediate data, but also by the correlated data given in preceding papers of this series, by the data afforded by the studies of the chemical differentiation of bone during growth (20) (21) (22), and by the pertinent correlation coefficients of the adult animal.

The weight correlation between hypophysis and ovary is  $0.443 \pm 0.049$  when the general factors for organ size carried by the body weight and the influences assumed to be exerted by the other secretory glands have not been held constant by the method of partial correlation. Although the value drops to 0.223 when body weight is held constant it is still positive and valid. This shows that there is a weight association which is independent of body size. Correlating this with the fact shown in the preceding paper (17) that the growth response of the ovary to thyroid deficiency is almost entirely due to its dependence on the effectiveness of the general growth processes of the body, it is clear that the parallelism of the hypophysis with the body in weight is determined by its weight association with the ovary, rather than by its dependence on the growth factors of the body as a whole. That is to say, the ovary is the determinant of the post-pubertal parallelism of the response of the hypophysis and body weight to thyroid deficiency.

It is therefore evident that the reaction of the hypophysis in the female is not inconsistent with the idea of a specific secretory relationship of this gland to thyroid disturbance.

Turning now to the sex comparison it is seen from Chart 1A that no evidence of pubertal influence on hypophyseal reaction is present in the males. Consistent with this is the fact that there is no weight association between testis and hypophysis in the adult male when body size influence is held constant. The first order coefficient is -0.010.

The consistency of the data leads to the conclusion that the secretory relationship between thyroid and hypophysis in the male is largely uninfluenced by gonadal secretory activity. Hence the intervention of the gonad in the female is a sex-specific phenomenon.

Further sex-specificity is shown on Chart 2A where the response of the hypophysis of the males is compared with that of the females at each of the stated ages. It is seen that regardless of direction the degree of response is greater in the male than in

the female in all save the 65 day old series. Moreover, consistent hypertrophy of the hypophysis follows thyroid removal in the male but not in the female.

A similar trend of sex difference in response follows thyroid feeding. Hoskins (23) found that under such conditions the hypophysis of the male tends to be heavier while that of the female tends to be lighter than the normal control. The combined observations of Herring (24) and Hewitt (25) are in agreement with the findings of Hoskins.

These facts indicate that the specific relation of the hypophysis to thyroid disturbance is less influenced by sex-conditioned factors in the male than in the female. Consistent with this conclusion is the fact that there is no specific gonad-hypophysis weight relation in the normal adult male, while in the female a small but validly positive association exists. The 5th order coefficient is  $-0.070 \pm 0.051$  in the male and  $0.151 \pm 0.049$  in the female.

#### THE EFFECT OF PARATHYROID DEFICIENCY

On Chart 1C and D the growth of the hypophysis is compared with that of the body in weight after parathyroid removal at the stated ages.

It is seen that the growth of the gland is consistently retarded in both sexes in all groups. The course of the change in degree of retardation with change in age at time of the initiation of the parathyroid deficiency is quite the same for the hypophysis as for the body weight in both sexes save in the 65 day old series of females. This parallelism is proof that the growth of the hypophysis is not specifically related to parathyroid activity, and that the retardation which occurs is due to the dependency of the organ on the effectiveness of the growth processes of the body as a whole.

Consistent with this is the fact noted earlier that the coefficient of correlation between hypophysis and body weight is high and positive in the adult rat of both sexes.

There is a general trend for the retardation of the hypophysis to be less than that of the body weight. This difference is merely the expression of the characterizing difference in the metabolic processes concerned in growth of the hypophysis from

those of the body as a whole with respect to the lowered nutritional level produced by parathyroid deficiency. It is not due to any hypothyroid condition, for as Table 3 shows, the weight of the thyroid per unit body weight of the tests is not consistently different from that of their controls of the same age series.

The degree of difference is most marked at and after puberty in both sexes. This increase is further evidence for the belief stated in previous papers that the onset of sexual maturity determines profound changes in the physiological processes of all parts of the body.

The non-conformity of the organ with the body weight in the females of the 65 day old series is attributable to the specific secretory relation between ovary and hypophysis. This relation

TABLE III

THYROID WEIGHT PER UNIT BODY WEIGHT OF THE PARATHYROIDLESS RATS AND THEIR CONTROLS. THE VALUES FOR THE THYPAR CONTROLS ARE ALSO GIVEN TO SHOW THE NORMAL VARIATION. ALL VALUES FROM RATS 150 DAYS OF AGE.

	MALES			FEMALES		
	Controls		Tests	Controls		Tests
Age Series	Thypar*	Parathy*	Thypar	Thypar	Parathy	Parathy
23	1.03	1.12	1.16	0.96	0.94	0.89
30	0.74	0.77	0.69	0.89	0.96	0.88
50	0.88	0.89	0.78	1.11	0.96	0.95
65	1.02	0.91	0.82	1.01	0.94	1.00
75	1.33	0.86	0.90	1.31	1.03	1.04
100	0.90†	0.90	0.93	0.97†	0.97	0.87

\* "Thypars" refers to animals from which both thyroid and parathyroid glands have been removed; "Parathy" indicates parathyroid removal alone.

† Same controls for Thypars and Parathys.

has been noted in an earlier paragraph and the present record serves to substantiate its validity. That no similar reaction is shown in the male is further evidence in support of the belief, to which the pertinent correlation coefficients give additional support.

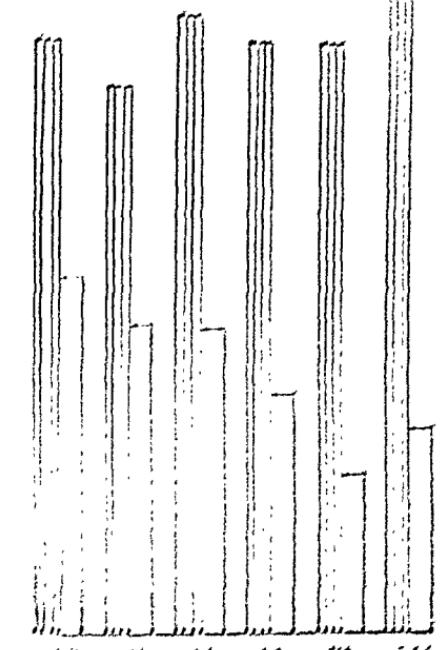
On Chart 2B the growth response of the hypophysis to parathyroid deficiency in the male is compared with that in the female. The retardation tends to be less in the female than in

the male. This is better explained by the fact that the pituitary is the chief factor in the regulation of the growth of the body. The smaller these variations since in this animal the pituitary glands were removed, it is evident that the pituitary gland is the chief factor in the regulation of the growth of the body.

### HYPOTHYROID HYDRO

Chart 8A-28738172

(A)



interpretation of the growth results of thyro-parathyroidectomy in terms of thyroid deficiency alone.

#### SUMMARY AND CONCLUSIONS

A report and an interpretation of the growth relation of the hypophysis to the thyroid apparatus is given.

The data lead to the following conclusions:

1. Thyroid deficiency conditions a consistent hypertrophy of the hypophysis in the male but not in the female.

2. The size and presumably the activity of the hypophysis is specifically related to the activity of the thyroid when this exceeds the usual limits in either direction.

3. This relationship is conditioned by gonadal ineretary activity in the female but not in the male.

4. There is no specific growth relation between the hypophysis and the parathyroids

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## REGENERATION OF THE THYROID, AN EXPERIMENTAL STUDY\*

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Wagner in 1884 first reported hypertrophy of the remaining lobe of the thyroid following lobectomy. Wagner's observation was based upon the appearance of the gland and not upon microscopic examination. He made only two experiments, one upon a dog and one upon a cat. Horsley, in 1886, confirmed Wagner's report and showed that there were both hyperplasia and hypertrophy of the epithelial cells with plication of the walls of the acini. Horsley states that he did not find any increase in the cells of Webber and saw no evidence of metamorphosis of embryonic tissue into acini. Cristiana observed hypertrophy in a small transplant of the thyroid gland when the greater portion of the gland had been removed. Manley and Marine have since reported that if iodine is given to the animals this hypertrophy will not occur.

Halstead's work first reported by Welch in 1888 and later by Halstead in 1896, was more extensive than anything preceding. He established the fact that: 1. Total extirpation of the thyroid gland is followed by an early death; 2. Dogs will survive if at least one-eighteenth of the thyroid substance is left; 3. Puppies from females having had one lobe or more removed, have goiter at birth; 4. Thyroid enlargement may follow infection. Halstead evidently removed the parathyroid for his description of death from total extirpation is very suggestive of parathyroid tetany. All puppies from females which had one lobe or more removed had goiter. There was no goiter in the puppies from females which had not been operated upon. This enlargement should not be regarded as an inherited goiter but rather as a fetal enlargement due to the attempted functioning of the thyroid in utero because of insufficient thyroxin in

\* Read at the Tenth Annual meeting of the Association for the Study of Internal Secretions, Dallas, Texas, April 20, 1926.

the mother's blood. From Halstead's paper, apparently the removal of a portion of the thyroid of the male had no effect upon the puppies.

Halstead believed that the hyperplasia occurred in the follicular cells, but in one of his pictures there is a very definite hyperplasia of the interacinar cells of Webber. (Fig. 1.) In describing the blood vessels, he states that they differentiate epithelial cells in what might otherwise be a jumble of interfollicular cells without arrangement, by surrounding primitive follicles. but from his picture and description it would seem

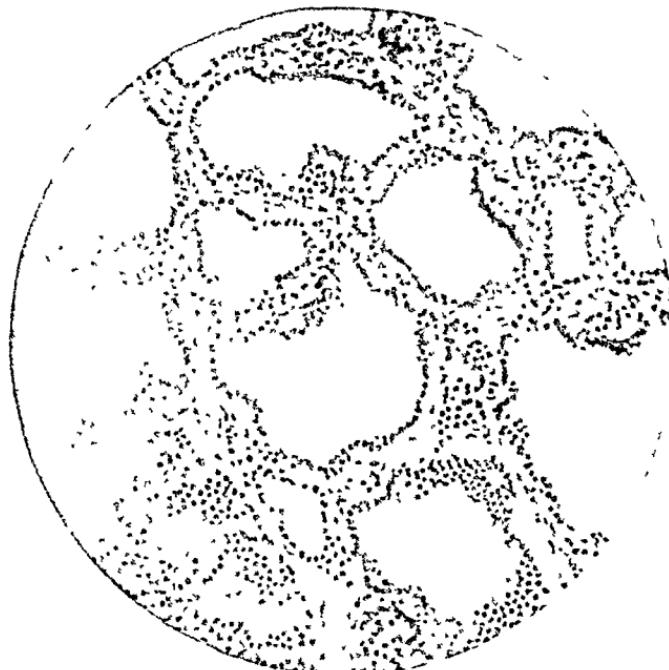


Fig. 1. Hyperplasia interacinar cell of Webber. From Halstead's publication in 1896.

more probable that these were primitive follicles developing as a result of the hyperplasia of the interacinar cells. He also describes definite hyperplasia of the follicular epithelium such as is seen in exophthalmic goiter. This was accompanied by a decreased thinning and vacuolization of the colloid.

Hunnicutt did not obtain the same results as did Halstead. In 59 experiments upon dogs, hyperplasia developed in only three. Marine accounts for the difference between Hunnicutt's and Halstead's work on the basis of the use of iodine as an anti-septic by Hunnicutt but not by Halstead.

Marine, in a paper written in 1907, concludes that hyperplasia of the thyroid is a physiological reaction in a deficient gland and that colloid goiter is usually preceded by a stage of hyperplasia and in its uncomplicated form is to be regarded as a quiescent state of the hyperplastic form. He also showed that the giving of iodine to dogs with the hyperplastic form, resulted in colloid secretion.

Loeb in 1919, in working upon guinea pigs, found that hypertrophy occurred after the greater portion of the gland had been removed. This hypertrophy might appear during the



Fig. 2 Colloid goiter (human) with hyperplasia and the formation of acini and definite tubules interacinar.

second week, but usually appeared between 15 and 18 days. Cell multiplication usually ceased at the end of 22 days, but might persist for 30 days. The evidence of hyperplasia persisted for some time and could often be seen in the acini after four or five months. New formation of colloid occurred after six or eight weeks, having at first a viscid characteristic such as is seen in hypertrophied glands. Quantitative relationship was found between the amount of thyroid removed and the amount of hypertrophy, but the same order of change and the same lapse of time occurred regardless of the amount removed. Abor-

tion usually, but not always, followed complete extirpation in pregnant guinea pigs, but did not promote compensatory hypertrophy in either the mother or the fetus.

Crawford and Hartley, in a recent paper in which they studied the effect of lobectomy upon the remaining lobe, found that within two days there was a beginning increase in colloid secretion, which continued to increase until the seventh day, at which time the acini were increased in size, distended with colloid and the epithelial cells were flattened. Following this, com-

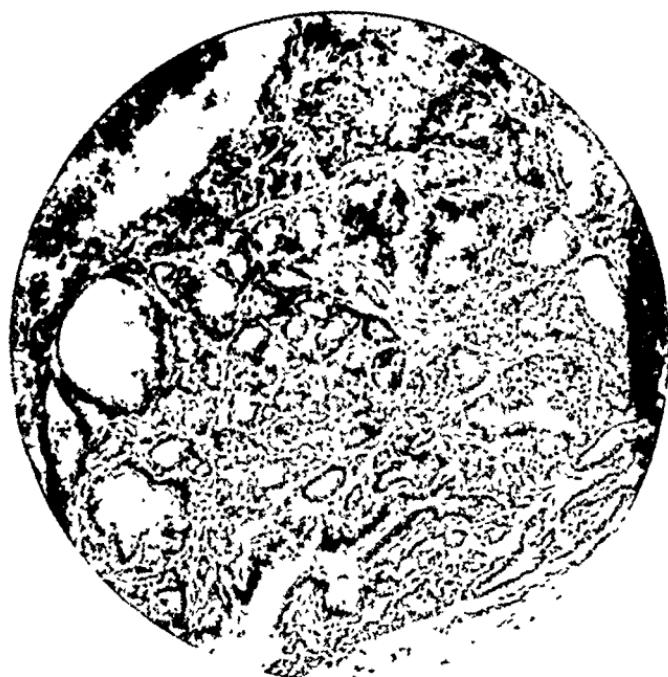


Fig. 3 Hyperplasia with the formation of acini and definite tubules in a colloid goiter of long standing.

pensatory hypertrophy took place. The evidence of compensatory hypertrophy was present after three to four months.

In a previous paper I have traced the development of adenomatosis or diffuse adenomatous type of goiter from the hyperplasia of the interacinar cells, first described by Webber, showing first the development of undifferentiated cells, second the formation of fetal acini, third the beginning of colloid secretion, and fourth the formation of adenomatous masses. In the same paper is shown the development of new acini within old acini from the epithelial cells lining the acini, the process being the same; first the undifferentiated cells, then the fetal acini,

then the beginning colloid secretion, and finally the larger acini containing more colloid.

A study of colloid goiter in the human shows that at first there is an increase in the amount of colloid in the acini. With the distention of the acini the cells become flattened, due partly to a stretching because of the increase of circumference of the acini and partly to increased intraacinar pressure. In patients with a colloid goiter of long standing there is found an increase in the epithelial cells between the acini. At first they present

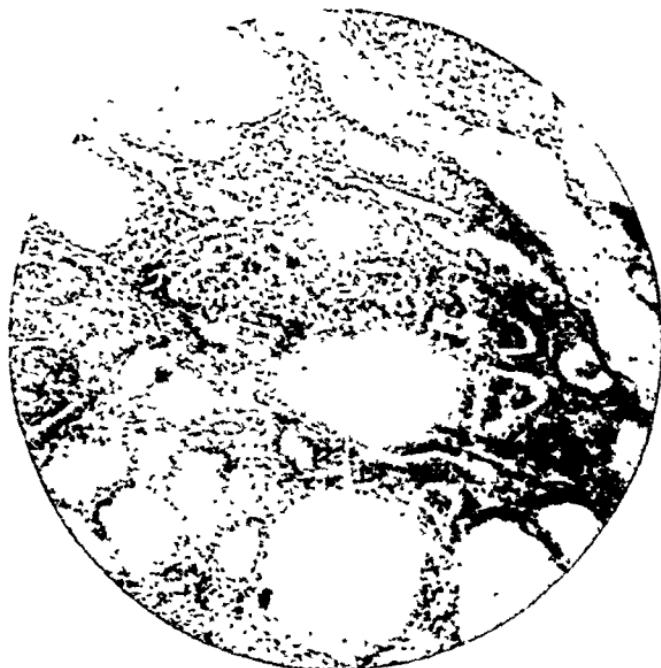


Fig. 4. Colloid goiter (human) with hyperplasia and new acini formation.

an undifferentiated appearance, sometimes being arranged in a columnar tubular-like structure (Figs. 2 and 3), suggesting the mode of development of the fetal thyroid. This is later followed by the formation of typical fetal acini (Fig. 4), and still later by the secretion of colloid, showing that the acini have taken on physiologic activity. Sometimes new acini are formed within the old acini from the intraacinar cells, as previously mentioned. When this occurs one finds a more or less pyramidal growth within the acini. The more central cells present an undifferentiated appearance; immediately below this is a beginning acinar formation presenting a fetal type of acini; below this the

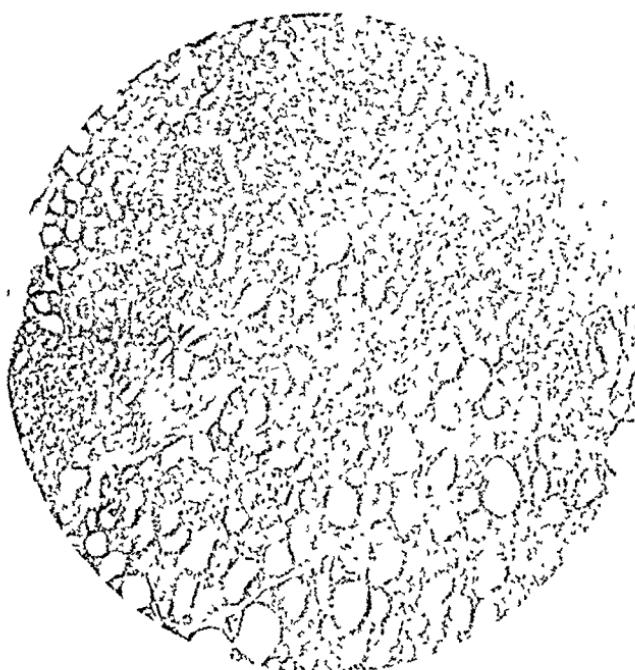


Fig. 5 Normal rabbit thyroid before partial thyroideectomy.

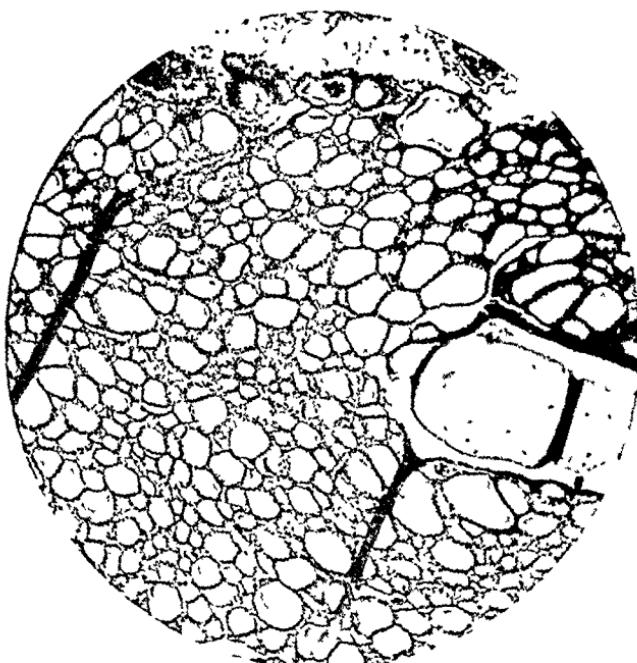


Fig. 6 Increase in colloid following partial thyroideectomy. (Same rabbit as Fig. 5.)

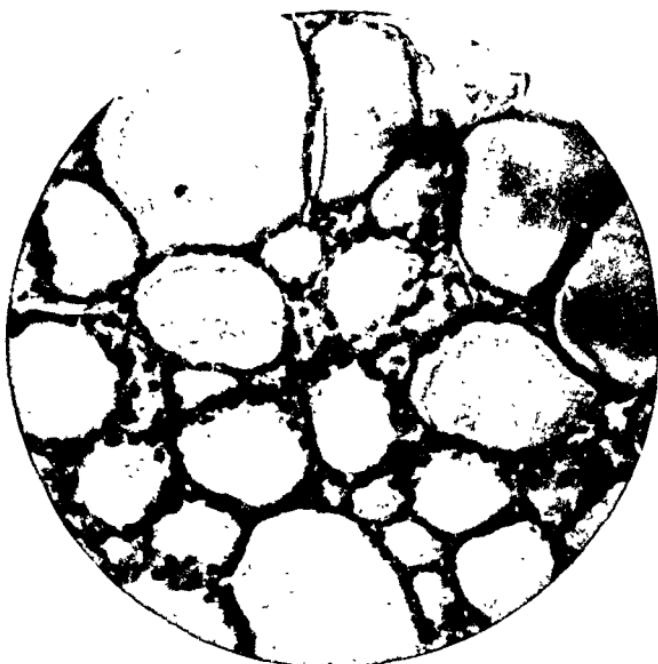


Fig. 7. Hyperplasia cells of Webber in rabbit's thyroid following partial thyroidectomy.

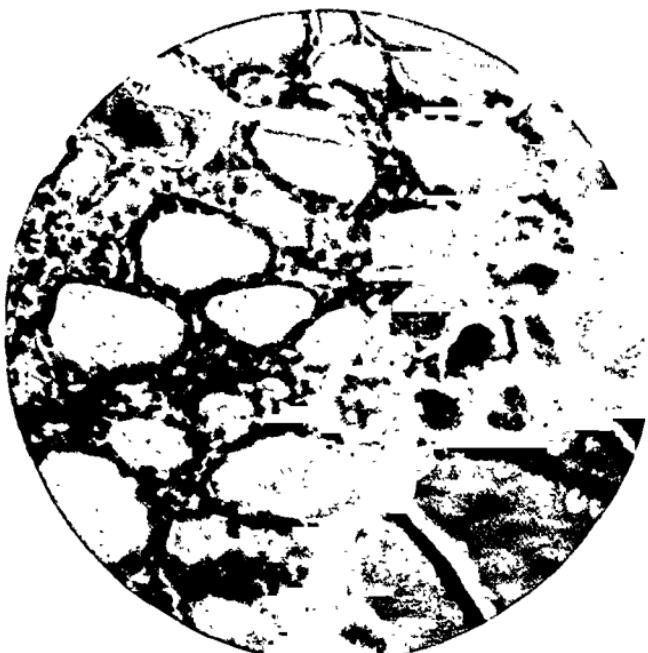


Fig. 8. Hyperplasia interacinar cells of Webber (rabbit) following partial thyroidectomy.

acini show the evidence of colloid secretion, and next to the old acinar wall, definite typical acini are to be found.

In operative work upon goiter it is the custom of most surgeons to remove all but a very small portion of thyroid substance along the posterior portion of the capsule. Many if not all of these patients later have an increase in the amount of thyroid tissue as determined by palpation. In some of them compensatory hyperplasia following the operation continues

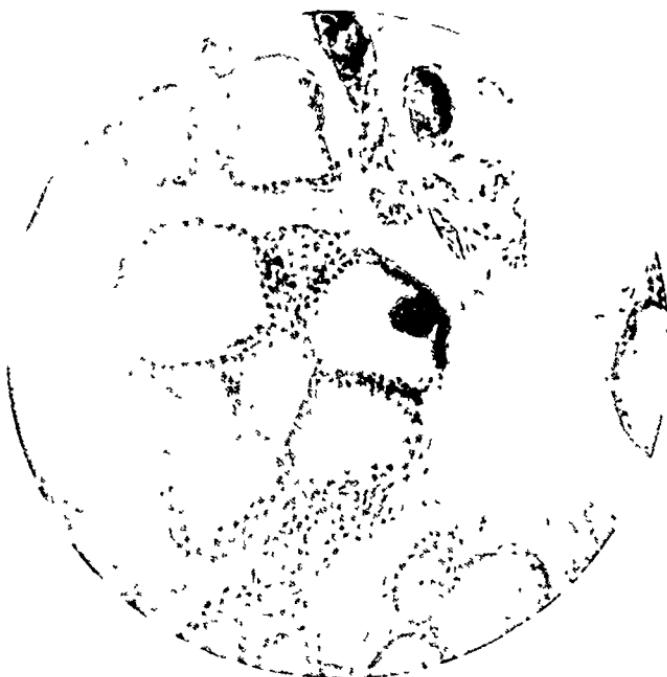


Fig. 9. Formation of new acini within old acini (rabbit).

until another goiter has developed. It was with the purpose of determining, if possible, the mode of regeneration following such operative procedure that experiments have been planned to show the effect upon the thyroid when one-half to three-fourths of the total gland substance has been removed. This paper is based upon that portion of the work which has been completed. A subsequent paper will report the balance of the work.

All of the work has been done upon rabbits. The entire right lobe was removed in all, and in the majority one-half of the left lobe also. The rabbits were permitted to live over periods of time varying from two days to ten weeks. They were then killed and the remaining portion of the thyroid gland was re-

moved and sections were made and compared with those made from the first portion removed. A study of the sections showed that in eight there was no change in the thyroid as the result of the removal of at least one lobe. In four there was an increase in colloid but no other apparent change. In one of these the colloid was vacuolated. In four there was hyperplasia of the interacinar cells (Figs. 7 and 8) with definite formation of fetal acini in one (Fig. 9). In one of these there was hyperplasia in the interacinar cells with the formation of new acini within the old acini in a few places.

In one-half there was practically no change as the result of the partial removal. This we interpret to mean that there was a sufficient amount of thyroid tissue left to meet the needs of the rabbit so that there was no demand thrown upon it for more secretion and, hence, no need of regeneration. In one-half, however, changes were observed, the most common one being an increase in the amount of colloid in the acini. This agrees with the findings of Crawford and Hartley, who state that the first change is an increase in colloid and is at variance with the opinion expressed by Marine that the first change is a hyperplasia. We interpret the findings in this group to mean that with the increased cellular activity a sufficient amount of thyroxin was secreted so that regenerative changes did not occur. In four rabbits there was a definite cellular hyperplasia occurring in the interacinar cells. This was evidenced mainly by an increase in the number of these cells but also in the formation of new acini. In one of these there was seen new acini formation within the old acini.

#### SUMMARY

In an incomplete series of experiments on sixteen rabbits partial thyroideectomy was performed. It was found that, first, so long as there is a sufficient amount of thyroid gland left to supply the necessary thyroxin to the animal there are no changes in the gland as the result of removal of same; second, that when a sufficient amount of thyroid substance is left so that stimulated activity on the part of the cells can supply enough thyroxin, regeneration will not take place and the increased cellular activity is shown only by an increase in colloid; third, that when there is not enough thyroid left to meet the needs

of the animal, hyperplasia takes place, developing usually from the interacinar cells of Webber, but also from the intraacinar cells, and in each case new acini are formed.

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# THE DEVELOPMENT AND NATURE OF THE SO-CALLED TOXIC ADENOMAS\*

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The interpretation of the meaning of the changes which take place in the so-called toxic adenomas is much more than of academic importance. If there is a hyperplasia leading to hyperfunction we are justified in the hope that a regression to the normal may take place. If it is a degeneration, then a restitution to the normal is out of the question. That any surgical procedure which leaves part of the diseased organ is not ideal surgery goes without saying. What comes of the part remaining after operation is not known. All surgeons frankly admit that cures are not complete in a certain proportion of cases. What ultimately becomes of the cured cases only the future can tell. Why some are not cured is a matter of immediate concern. What proportion of the "cured" ones remain well is still a matter of speculation, for we know that some patients remain symptom-free for a number of years and then they are sick again. Little thought has been given to this class of cases. These problems make it quite likely that new viewpoints are needed before we can advance much in the surgical management of goiters.

The first lap in the study of this problem is to determine the meaning of the degenerative changes which take place in colloid goiters, and the factors active in the production of the toxic manifestations. There is much talk about the active and resting stages, the regression to normal and the like. Much of this is based on speculation. Those who have experimented with the resection of goiters know how confusing the results are. One experimenter finds there is a hyperplasia of the remainder of the gland. Another finds that hyperplasia does not take place—and explains the divergence of results on the ground that the animal's neck was painted with iodine. Such attempts to force the results of experiments into harmony is enough to make the judicious grieve. Viewed broadly, one is compelled

\* Presented at the Tenth Annual Scientific Meeting of the Association for the Study of Internal Secretions, Dallas, Texas, April 20, 1926.

to admit that experimentation on animals has as yet not succeeded in permitting the deduction of any general laws. Clinical evidence is still the most fruitful source of information in determining what happens in the human being.

We are greatly in need of records of studies of the parts of glands remaining years after the removal of the most of the gland. Autopsies in such cases are greatly needed. There is accumulating evidence that, in many, a state of myxedema is approached and is preferable to the presence of part of a crippled gland. Some of my myxedematous patients have been under observation 30 years and more and are living in perfect health and contentment. So impressive are such cases that one must ask himself whether or not a grain a day of bouvine thyroid is not a better protection against senility than a dependence on our own aging thyroids. At least it is safe to assert that a surgical myxedema is not a calamity to be feared, when we face the severer forms of thyroid gland malfunction.

Working with goiters it is necessary sometimes to stop and inquire if we are working with symbols or real facts. The things we know for certain are few. The one certain thing is that myxedema is relieved by the constant use of thyroid extract. Nearly as certain is it that a typical case of exophthalmic goiter is associated with proliferation of the epithelium of the acini. Quite constant is the relation of the "toxic adenomas" to long existing goiter. From the purely surgical standpoint we know nothing as to etiology. The exophthalmic type is believed to be more or less a constitutional condition with local manifestations in the thyroid gland. To this surgery has to answer that when Basedow patients are operated on early and as completely as the surgeon dares, keeping in mind only the recurrent nerves and the parathyroids, the results are complete and permanent. This makes it appear that the real seat of the trouble lies in the thyroid after all. Long existant exophthalmic cases are associated with all sorts of general symptoms which are not wholly relieved by operation. Once an exophthalmic patient has undergone a remission irremovable complications may appear. These are looked on as primary and the goiter as secondary, but this is erroneous in the light of the results of early, bold surgical treatment.

It is of interest to inquire whether the injury is done by the imperfect colloid which forms during the height of the disease, or if it is done by the hypersecretion of the epithelial cells. Those that have degenerated areas are the ones which do not give good results after operation.

If we look at the life history of the so-called toxic adenoma we learn that it is generally agreed that a long period of time elapses from the beginning of the goiter to the beginning of serious general symptoms—a state which we symbolize by the word “toxic.” This period may be stated in round numbers as sixteen years. This period is dated from the time the patient first becomes aware of the presence of the goiter, which means that at that time the goiter was already of considerable size. As to when the increase in size of the goiter actually began there is little evidence. What the goiter was doing during the years of its “innocent” adolescence has not been sufficiently scrutinized. Worse still, most writers seem to imply that the goiter exerts its baneful influence with a certain degree of suddenness. Observation of these colloid goiters through the decades convinces me that there is nothing sudden about it. The various symptoms are in evidence years before the patient is aware of it. I imagine that the fabled camel complained that some guy dropped a load of straw on his back causing a fracture of the vertebrae. Now if he had been observant he would have known that the accretion of straw was gradual and all save the last straw was innocent of harm. It would be safe to say to a camel accumulating a like load that if he does not stop the procedure somebody is going to drop on one straw too many. So we can say to patients with the old colloids, “If you don’t get rid of it, it will get you sometime.”

I have been feeling goiters and sectioning goiters in this community more than 30 years. This experience convinces me that an attempt to distinguish between adolescent, the slightly toxic and the multilobular colloids is no more sane than attempting to classify the separate weeks in typhoid fever as separate diseases.

I can multiply such pictures as the following: A young girl has an enlarged gland, a perfectly innocent thing, and will disappear (30 years ago). That the girl was nervous and had dysmenorrhoea was unfortunate (30 years ago) child birth would

relieve this; 20 years ago the Battie operation; 10 years ago dilatation, curretage, the stem pessary or the removal of a "chronic appendix"). But the goiter was innocent. With the passing of years and the advent of pregnancy the goiter reappeared, uniform in outline, soft or elastic in consistency, otherwise innocent. Intimate acquaintances noted the patient was more irritable than formerly but she being possessed by (or with) a husband and children, who needs to look to the thyroid as a cause of nervousness? The goiter shows an irregularity here and there and in time becomes lobulated. It is now a lobulated colloid. Sometime between 34 and 55 the patient notices some shortness of breath, irritability, loss of weight and perhaps more serious symptoms. But there are the children in society and the enlarging prostate all calculated to disturb mother's rest (thus we thought 30 years ago). These symptoms increased and anorexia supervened, rapid emaciation and mother was buried, innocent goiter and all, now these thirty years ago.

We now know that the demise of the hypothetical case was caused by a toxic adenoma. But we are as ignorant as ever as to the actual cause of death. Symbolized complacent ignorance.

The only means we have of charting the course of such cases is to examine a large number of goiters removed from patients representing the various stages of the disease and correlate them with the clinical symptoms.

Histologically we have in the early stages a goiter which shows an increase in the colloid. The acinal epithelium shows but little change. Those associated with nervous symptoms (and usually dysmenorrhoea) we find some degeneration of the colloid, some flattening of the acinal epithelium and some increased prominence of the interacinal cells. During the long, innocent stage when the gland is becoming nodulated a most varied picture is encountered. The one constant thing is that acinal cells are flat and obviously inactive. New glands form in the interacinal cells. These, too, have flat cells, obviously inactive. The colloid is degenerated. The connective tissue is increased in amount and has undergone various types of degeneration. Epithelial cells are found in groups in masses of degenerated connective tissue. Such cells certainly are not capable of performing any function. Such pictures as these are found in the

old innocent goiter and the toxic adenomas. There is no sharply dividing line.

It has been assumed that it is the gland proliferation which is responsible for the constitutional symptoms. This is pure assumption. Against this assumption is the very pertinent fact that these are harmed by iodine while the cell-active type (the "Basedows") are helped by this drug. It is not explained how this could be if both types owe their activity to an increase of the acinal epithelium.

It must always be remembered in this connection that a true "Basedow" may be implanted on an old colloid goiter. The clinical findings and the history should enable one to determine with a considerable degree of accuracy which are the combined cases. The histology shows such combinations clearly. This becomes more obvious when the course of the disease after operation is compared with the slide from time to time, for neither our interpretation of the slide nor our judgment of the clinical conditions is infallible.

The important fact in this connection is that the whole gland of the toxic adenoma is diseased. The histology indicates that it is injured beyond repair. According to present methods we remove a part of the diseased tissue. This is unsurgical. The demands of ideal surgery dictate that the whole of the diseased tissue shall be removed. The question is, are we able at this time to meet the ideals in the surgical treatment? The result is a myxedema. This myxedema can be controlled by the use of thyroid extract. There are no more comfortable persons than those myxedemics who take their grain a day. This is better than to allow the patient to depend on the remaining part of a hopelessly crippled gland. I believe the facts will substantiate this statement. We need more detailed knowledge, both in pathology and clinical diagnosis, before we can speak with assurance. Besides, the technical difficulties in removing all the gland are by no means small. Something more exact than the grab and cut method commonly employed in thyroideectomy must be adopted. The recurrent nerves and the parathyroids must be spared.

Much work must yet be done in which the whole gland is deliberately removed. The production of myxedema is still considered an actionable offense, and no one cares to publish evi-

dence for the use of the attorneys for the plaintiff. The law requires the surgeon to exercise the skill common to the profession in his environment. To do better than the average is as great an offense as to do worse.

## GOITER: CURRENT ERRORS IN ETIOLOGY AND TREATMENT

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PHILADELPHIA

A goiter is not merely a lump on the neck, but a local expression of causes originating or having originated elsewhere in the body. Also, contrary to popular notion, the cure of goiter is not necessarily by means of iodine or by thyroidectomy. In a prolonged study of the subject, with a series of thousands of cases, I have found that a large percentage of patients seen have already been iodized, thyroidectomized, or both, with detriment to the individual.

The reason why treatment of goiter is still largely chaotic is that the doctor's span of existence is too short to know everything about everything in medicine. The subject of goiter, because of its broad implications with regard to pathogenesis and subjective and objective symptomatology, frequently requires a most widespread regime of therapeusis. Goiter is a specialty and is as large and exacting as any in medicine. Even the few goiter specialists to be found in this country have still very much to learn on this subject. Each day presents new problems requiring solution.

There are several common misconceptions on the goiter question.

*That we can dispense with the major portion of the thyroid gland* is a fallacy employed daily by thyroidectomists who do not differentiate between surgical and non-surgical goiters. An encapsulated, truly neoplastic goiter must be removed in such manner as best befits the case in hand, and a careful thyroidectomy is the only treatment acceptable.

On the other hand, *simple hypertrophy* and *colloid goiters* indicate the need for *more* thyroid secretion, and the basal metabolism in these patients indicates a tendency toward hypothyroidism. Such goiters should be treated not by surgery, but by the elimination of discoverable causal factors, and, if necessary, the cautious administration of thyroid hormone to rest

the organ. *Puberty hyperplasia* is a status in which the individual presents a strong susceptibility to Graves' syndrome. Here, too, casual relationships should be sought and the proper corrective measures instituted by an internist. In *exophthalmic goiter* (Graves' syndrome) nature resents thyroidectomy as evidenced not only by the high operative mortality rate (statistics notwithstanding), and lack of clinical cure, but by return of the goiter. It is here especially that surgeons claim the need for the removal of three-fourths, five-sixths, seven-eighths, and recently even the entire thyroid gland! This latter procedure has just been advocated by Gilman and Kay.\*

If, as Crile says, the thyroid is what makes life worth living, then life is worth living only in proportion to the amount of normal thyroid structure possessed by the individual. The hyperplastic thyroid may be compared to a loaded sponge which unloads itself, shrinking to its former normal size and structure following properly applied non-operative measures *not necessarily directed to the thyroid itself*. If we could follow in our mind's eye the physiological variations of thyroid activity, we should see this organ's function waxing and waning with the mental and physical actions of the person's daily life. In order successfully to cope with problems in the fight for self-preservation and the strife incident to the march of civilization, one must possess sufficient thyroid structure and function during physiological stress and strain. Without it we fall by the way-side. How can the surgeon reconcile himself to these facts and at the same time claim that an individual can "get along" with a tiny fraction of the amount of thyroid endowed him or no thyroid at all? Such an attitude is an assumption on the part of the thyroidectomist that he knows more about the mystery of life's processes than does nature herself. The fact remains that sooner or later those who have been considerably or completely thyroidectomized become a burden to themselves and society. Even sheep's thyroid is incapable of satisfactorily substituting entirely for the human hormone.

*That goiter is necessarily a disease of the thyroid gland is not true.* It, therefore, must not be treated as a local condition. With few exceptions, all goiters begin as local expressions of

\* Gilman, P. K. & Kay, W. E.: Total thyroidectomy in thyrotoxicosis of the exophthalmic type. Am. J. M. Sc. (Phila.), 1926, 171, 239-245.

disturbances elsewhere in the economy. In regions away from goiter belts simple hypertrophy and colloid goiter are usually due not to lack of iodine, but to the premenstrual status, adolescence, pregnancy, heredity, focal and general infections, intestinal intoxication, pelvic neoplasms, and other conditions away from the thyroid gland. Untreated, thyroid swellings of this sort occasionally disappear spontaneously. Most often, however, they persist, and in the course of time pathological changes within the thyroid may so change the mass as to give rise to adenomata or cysts. Thus we now have a kind of local condition requiring thyroideectomy even though the primary cause may have disappeared. Originally, however, the goiter was not a disease of the thyroid, requiring not local attention, but a correction of the underlying causal factors.

*That there are two kinds of goiter, simple and toxic, is another common misconception.* Goiter may be toxic, giving rise to thyrotoxemia when in a state of hyper-secretion, but there is no such thing as a "simple" goiter. Rather than "simple," we might use the term non-toxic in contradistinction to toxic goiter. A non-toxic goiter, though not secreting an excess of thyroid, is a rather complicated affair, as mentioned in the preceding paragraph.

*That all toxic goiters are cases of hyperthyroidism is not true.* There are four types of toxic goiter: (a) toxic adenoma, synonymous with hyperthyroidism; (b) puberty hyperplasia, synonymous with the pre-Graves' disease status; (c) diffuse adenomatosis, an uncommon condition about which more will be known in the future; and (d) exophthalmic goiter, synonymous with Graves' disease, Basedow's disease, Parry's disease, Flajani's disease, dysthyroidism, etc. Exophthalmic goiter is not, and is not due to, hyperthyroidism. A realization of this fact would put an end to much irrational therapeusis.

*That basal metabolic tests are infallible is an error* usually entertained by the enthusiastic laboratory man who has not sufficient opportunity to observe the human being under the stress and strain of thyroid dysfunction or of Graves' disease. Calorimetry is one of the most valuable laboratory aids. On the other hand, to depend upon it alone for diagnosis, as is frequently done, is a mistake. Rather would I trust the trained senses in the diagnosis of the presence and severity of hyper-

thyroidism, than a mere brainless instrument, the sources of error in the manipulation of which are numerous enough to fill a good-sized monograph.

I find basal metabolic determinations useful for *diagnostic* purposes in merely 5 per cent of cases. Calorimetry is useful in the determination of the *progress* of the patient under treatment in approximately 50 per cent of cases. The greatest value of basal metabolic determinations properly performed under ideal conditions lies in *confirmation of recovery*. Strictly speaking, the trained senses of the well equipped goiter specialist are sufficient to determine recovery; but there is an indescribable sense of ease and pride in knowing that basal metabolic determinations *confirm* the findings through the expert use of our senses.

*That all goiters require surgery is an error* that leads to unnecessary thyroidecomies and destruction of confidence of the laity in the medical profession. The *therapeutic classification* of goiter is the safest guide. This divides goiter into two classes: (a) Surgical goiter, requiring thyroideotomy; among these are such encapsulated neoplasms as adenomata and cysts; thyroid enlargements substernally or intrathoracically located or those of such size as to occasion marked pressure symptoms, likewise require surgery. (b) Non-surgical goiter, consisting of unencapsulated thyroid swellings such as simple hypertrophy, colloid goiter, puberty hyperplasia, and the hyperplastic thyroid of exophthalmic goiter or Graves' disease. These four types of thyroid swelling yield splendidly to a properly applied regime of non-operative therapy, and when erroneously thyroidectomized, not only present recurrence, but sequential constitutional derangement as well.

*That all rapid hearts in association with goiter are due to thyrotoxemia* is likewise not true. Tachycardia, in the presence of goiter, is usually due to the latter, but exceptions to this rule are numerous. (a) The patient may have paroxysmal tachycardia, or an organic heart lesion totally independent of the thyroid enlargement, the goiter occurring merely as an incident. (b) The subject of goiter may be suffering with a febrile condition accounting for the rapid heart action. (c) Extremely sensitive, apprehensive, or self-conscious patients who, under ordinary conditions have a perfectly normal heart rate, applying

to the physician for the treatment of an innocent goiter, may present such a flare-up of the heart rate as to give rise to the opinion on the part of the examiner that he is dealing with a case of "toxic" goiter. (d) An otherwise harmless thyroid enlargement but substernally or intrathoracically located, may give rise to so-called "mechanical goiter heart," due to circulatory and respiratory mechanical embarrassment because of the aberrant location of the mass. This latter status is most often confused with the "thyrotoxic goiter heart," the term applied to a heart under the influence of a hyperactive thyroid.

*That the medical treatment of goiter consists in the administration of iodine* is a fallacy responsible for more goiters than have ever been seen before. The use of iodine in the prophylaxis of goiter in endemic districts may be a useful procedure, though no doubt many persons receiving iodine in goiter belts are not susceptible to goiter and are therefore being unnecessarily drugged. Doubtless a fair percentage of small goiters occurring in goiter belts are due to a deficiency of iodine in air, food, or water, hence are curable by iodine therapy. Here, too, it must be remembered that goiters seen in endemic districts are not necessarily endemic goiters, but may be due to sporadic causes not dependent upon iodine deficiency.

The protagonists of iodine therapy in the management of goiter have committed a great error of omission. They omitted to qualify their statements and point out that iodine is only to be employed where it is reasonably certain that the patient is suffering from iodine deficiency. The *universal* administration of iodine, with its propaganda favoring the use of this drug indiscriminately, is a menace to the health of the community. Iodine is a potent drug, to be given only upon the advice of a competent physician—a medical man who is capable of passing judgment upon the needs of thyroid patients. Indiscriminate administration of iodine, coupled with self-drugging by many persons who purchase iodine or its proprietary compounds with a view to curing goiter, has been responsible for the growth of almost invisible thyroid enlargements into large, bulky goiters, and what is worse, simple, non-toxic goiters become those hypersecreting masses that bring about marked circulatory and nervous deterioration. The medical profession is beginning to awaken to this danger, and the sooner there is a concerted ac-

tion against this iodine propaganda and its legislative enactments, the better it will be for the American public.

*That exophthalmic goiter is the proper term for the syndrome observed* leads to erroneous diagnostic, clinical, and therapeutic implications, and hinders progress. A goodly percentage of sufferers from this disease present neither exophthalmos nor goiter, yet are suffering with the affection. To depend upon exophthalmos and goiter for diagnosis is harmful to the patient, as diagnosis is often unduly postponed and the appropriate treatment applied too late. Moreover, since goiter, when present, is merely an incident in this widespread syndrome, the disease being largely characterized not by hyperthyroidism but by nervous, emotional, circulatory, gastrointestinal, cutaneous and other evidences of a generalized neuro-endocrine imbalance, this disease should not be regarded as belonging in the category of goiter, but should be looked upon as a *constitutional* affection. Goiter is no more a primary element in the etiology and symptomatology of Graves' syndrome than is the enlarged spleen that of typhoid fever. Each is a secondary element, a defensive reaction in a generalized condition. Hence the term exophthalmic goiter should be discarded and the term Graves' disease employed for want of a better name.

*That the "medical" treatment of exophthalmic goiter consists of the administration of a drug such as iodine or quinine,* is a notion on the part of both internists and surgeons that gives rise to the entire difficulty with the therapeusis of Graves' disease. The internist, failing to cure his patient by the administration of a drug, concludes that "medical" treatment is a failure, and turns the sufferer over to the surgeon for thyroidectomy. The surgeon, recognizing the failure of "medical" treatment, proceeds to operate. But eventually, surgery having failed to produce cure, he attributes this failure to lack of "sub-totality" of thyroidectomy, and another operation is performed. Indeed, 30 per cent of sufferers with Graves' disease sent to me for consultation already present one or more scars of thyroidectomy, and are in worse plight than ever before.

The "medical" treatment of exophthalmic goiter should give way to what had best be termed the *nonsurgical management of Graves' disease*. This does not consist of the administration of a drug. It presupposes that the medical attendant

is thoroughly equipped to manage a patient of this type. The keynote to success in therapeutic management is strict individualization, with the administration of such measures as qualified rest, diet, medicaments, occasionally electricity, and psychotherapy permeating treatment in all directions. Having eliminated all discoverable causes, these measures are employed in suitable quality and quantity by the properly experienced internist for the proper length of time. In the event of unequivocal co-operation on the part of patient and household, complete, permanent recovery occurs within from six to twelve or fourteen months, the duration depending upon the chronicity and severity of the syndrome. Such a patient, taught how to eat, how to sleep, how to rest, how to work, and even how to think, is permanently restored to usefulness and happiness, and enjoys unprecedented health.

We cannot overestimate the importance of this topic. If we consider the vast number of goiter cases in our midst—at least 5,000,000 in this country—we cannot but hope that there will soon be a clarification of this enormous problem for both the medical profession and the lay public.

# PRESENT STATUS OF THE PROBLEM ON TRYPTOPHAN AND THE THYROID GLAND

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The hypothesis that "tryptophan is the mother substance of the thyroid hormone" (Cramer, 1923,), were it true, would be very significant. Physiologically, it would settle the complex problem as to the origin, genesis, and the nature of the thyroid hormone; and clinically it would justify the trial use of tryptophan deficient diet in the treatment of exophthalmic goiter (Harries, 1923). During the last two years evidences pro or con have accumulated. This paper summarizes all facts available in order to point out where this important question stands today.

## HISTOLOGICAL EVIDENCE

This has been studied independently and almost simultaneously by three groups of workers, all using the albino rat as the experimental animal. Their findings are more or less the same, but their interpretations are by no means in harmony with one another.

Cramer (1923) finds that rats on a diet rich in vitamin but poor in tryptophan develop "a very characteristic atrophy of the thyroid gland," which "does not occur in vitamin B deficiency." From this finding alone he concludes that "tryptophan is the mother substance of the thyroid hormone."

Chang (1925) confirmed Cramer's finding of atrophy in the thyroids of rats on tryptophan-deficient diet, but found similar thyroid atrophy in animals of parallel state of malnutrition brought about by restricted amount of *adequate* diet. Moreover, he was unable to demonstrate any change in the thyroids after daily subcutaneous injection of excessive amounts of tryptophan for a long period of time. Furthermore, when a heavier animal was put on tryptophan-deficient diet, and sufficient amount of tryptophan was given to maintain the body weight so that at the end of the experiment it was considerably heavier than its pathological controls, i. e., animals on chronic starvation and tryptophan-deficient diet alone, the thyroid was found

to be the nearest to normal structure of the three. On the other hand, where the final body weight of the tryptophan injected animal fell to the same level as those of its pathological controls, the thyroid was as atrophic as those of the other two in spite of the tryptophan given. He is, therefore, inclined to think that the thyroid atrophy in animals on tryptophan-deficient diets, as has been described by Cramer, seems to be due to the disturbed nutrition of the animal rather than the absence of a specific influence of tryptophan on the thyroid gland.

Abel, Bachus, Bourquin and Gerard (1925) report two co-existing findings in the thyroids of rats fed on tryptophan-deficient diet. In the first place, "the thyroid appears so nearly normal that it seems to obtain the amino acid from the blood plasma at the expense of other tissues, to the end to produce its secretion." In the second place, "it did exhibit a definite increased cellularity consistent with moderate strain," and "if this strain is long continued and severe," thyroid atrophy as described by Cramer follows. Their conclusion, therefore, agrees with Cramer, but the two different explanations based on two different findings of a same thyroid gland seem to be more improbable than contradictory.

The recent cytological work of Chang in collaboration with Dr. Wen Chao Ma, to be reported later, has corroborated his former findings satisfactorily.

At present we believe that the histological evidence from which this far-fetched hypothesis has been derived is untenable.

#### PHYSIOLOGICAL EVIDENCE

McCarrison (1924) claims that tryptophan, leading other amino acids studied, retards the metamorphosis of tadpoles, increases the colloid secretion of the thyroid and induces "ill-developed if not actually atrophic thyroids" among the smallest tadpoles. The size of the thyroid is increased with large vesicles by tryptophan, but decreased by other amino acids tested. The interpretation of these findings is not given.

The retardation of tadpoles' metamorphosis is not significant in terms of thyroid function, because Gudernatsch's phenomenon seems to be a test for some non-specific iodine compounds (Swingle, 1918, 1919, 1922, 1923, 1924). It is interesting to note here that the amino acids, for whatever reason

it may be, have a general reaction towards retardation of the tadpole's metamorphosis, which in turn might be responsible for the changes of the thyroid gland described.

#### CHEMICAL EVIDENCE

Weir (1925) has assayed 52 glands of exophthalmic goiter and adenomatous goiter, and has found that the average tryptophan content is approximately 3%, being higher than that of casein; but there is no definite relationship between this tryptophan content and the pathological type of the gland or the thyroxin content or the basal metabolic rate.

Most of the evidences to date are not in favor of the assumed importance of tryptophan in the thyroid gland function. Further physiological and chemical evidences are necessary to decide this question.

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## STANDARDIZATION OF PREPARATIONS OF OVARIAN FOLLICULAR HORMONE

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DETROIT

Allen and Doisy and their associates (1) in 1924 originated the "*rat unit*" as the standard by which the potency of preparations made from ovarian follicular fluid are measured. Their definition is as follows:

"Provisionally we wish to define a *rat unit* as the quantity of material necessary to induce estrus as judged by the smear method in an ovariectomized sexually mature rat weighing 140, plus or minus 20 grams. For physiological reasons we generally make three injections at intervals of 4 hours. The *rat unit* then is the minimum amount so injected which produces full estrus growth in the genital tract. Although we are convinced that this method of testing is roughly quantitative, we have not yet made a careful study of its limitations."

This *rat unit* as defined above is used as the standard of potency for preparations of ovarian follicular fluid made in this laboratory. Potency is expressed in number of *rat units per cc.*

In making use of the *rat unit* as a practical standard it very soon became apparent that it was necessary to know whether or not the minimal dose which would cause oestrus in a spayed rat varies directly with the weight of the rat. It was difficult to keep a large number of spayed rats of about 140 grams weight. Rats normally weigh 140 grams when about 3 months of age and grow so rapidly that in another month some of them weigh over 200 grams.

In this laboratory we have worked for several months on this problem. We have used rats from one month up to 12 months of age in order to learn if the age of the rat had a direct influence on the effectiveness of the ovarian follicular hormone. In normal rats one month of age injections of small doses of active follicular fluid extracts caused opening of the vaginal orifice and thickening of the vaginal mucosa, and cells obtained

from the vagina showed the forms characteristic of oestrus. As oestrus in such young animals is not physiological it did not seem advisable to use them in standardization. Female rats usually reach sexual maturity, as evidenced by the opening of the vaginal orifice, when two to four months of age. For practical standardization it is important to know that the female rats have normal reproductive organs and this opening of the vaginal orifice is the earliest indication of such normality. In the older age groups we have kept rats under examination for two weeks during which time vaginal smears were taken daily. Only rats were used which showed regular oestrous cycles.

In order to keep rats in a normal condition it is very essential that they be well taken care of. They are very sensitive to changes of temperature, so should be kept where the temperature is constant. They must not be crowded too closely together. In this laboratory only six or eight are kept in cages 21x15x12 inches. Rats will not have regular oestrous cycles unless they are given an adequate amount of food containing sufficient vitamins A and B. For our purposes we have found the Sherman ration (2) satisfactory. This has a great advantage over many other standard rations in that it is so easily prepared. It consists of whole wheat flour 65 per cent, whole milk powder 33 per cent, and sodium chloride 2 per cent of the weight of the flour.

Normal mature female rats when not pregnant and not lactating go through regular oestrous cycles so that oestrus occurs every four to eight days. After both ovaries have been removed the rats remain constantly in the resting stage, anoestrus. The operation of removing the ovaries is done under ether anesthesia. Either a single central abdominal incision or two lateral incisions may be made. It is not necessary to ligate the ovarian blood vessels. The incisions are closed by suturing in two layers with fine silk. The lateral incision method has the advantages that incisions less than one centimeter long may be used and the intestines do not have to be manipulated so much. Rats recover quickly from the operation and may be used in experiments in one week. In this laboratory smears are taken from all spayed rats each day so as to make sure that the rats are not having oestrous cycles without treatment. In the scores which have been operated in this laboratory there

have been two rats which began to have oestrous cycles several weeks after operation, showing that the ovaries had not been completely removed and regeneration had taken place.

In order to determine the oestrous cycles in the rats small moist cotton swabs are inserted gently into the vaginas. Glass slides are smeared with these cotton swabs. The cell forms are differentiated by staining with haematoxylin and eosin. (Mayer's haemalum and .5% aqueous solution of eosin.)

According to Long and Evans (3) the five stages of the oestrous cycle are characterized as follows:

Stage I—Pro-oestrus. Before heat begins. No sexual excitement. Vaginal smears show small epithelial cells with nuclei. No leucocytes.

Stage II—Oestrus. The heat period. Copulation accepted. Vaginal smears show large squamous cells without nuclei. No leucocytes.

Stage III—Late Oestrus. The heat period is over. No sexual excitement. Vaginal smears are thick and cheesy, containing clumps of large squamous cells without nuclei. Late in this stage there may be some large epithelial cells with nuclei. There are no leucocytes.

Stage IV—Metooestrus or Postoestrus. The stage of degeneration and leucocytosis. Vaginal smears show moderate numbers of polymorphonuclear leucocytes, squamous cells and large epithelial cells.

Stage V—Anoestrus or Dioestrous Pause. The resting stage. Vaginal smears show polymorphonuclear leucocytes as the predominating cells and moderate numbers of large epithelial cells and strings of mucus.

In this laboratory a reaction to injections is called *typical oestrus* if a smear shows the squamous cells of stage II without a single leucocyte being found. If even one or two leucocytes are found in the stage II smear the reaction is called *atypical oestrus* and it is considered that an insufficient quantity of the hormone was injected.

Allen and Doisy (4 and 1) developed a practical method of obtaining an active extract from the follicular fluid. They precipitate the proteins with alcohol and dissolve and purify the active fraction in ether, acetone and other lipoid solvents. Their final product is a heavy, oily substance which they dis-

solve in corn oil. In our laboratory this method has been modified, so as to be applicable to quantity production, by Messrs. Adrian Thomas and F. H. Tendick. As oils are not readily absorbed when injected subcutaneously they have supplied it in the form of an aqueous colloid solution of the emulsoid type, which is readily absorbed after subcutaneous injection.

The preparation used in the experiment reported in this paper is of such concentration that each cubic centimeter represents the activity of 6 cc. of fresh follicular fluid, obtained from hog ovaries. The potency per liter of the fresh fluid is 1250 *rat units*, which is within the range which Allen and Doisy (1) have reported as the potency obtained by them in their extracts.

Allen and Doisy (1) recommended giving three injections of their oil solution at four-hour intervals when standardizing preparations on rats. As our aqueous solution is absorbed so readily it was deemed advisable to spread the dosage out over a longer period. After considerable experimentation we decided that our preparation gave the best results in rats when given in eight separate injections, four each day on two successive days. When the tests are made according to our method oestrus often occurs on the fourth day of the experiment. Often typical oestrus cell forms, with no leucocytes present, are found in the vaginal smears for only a few hours. For that reason we take several smears at intervals as follows: one on the first day of injection, one on the second day, three on the third day, and three on the fourth day.

Table I gives the data of one experiment which was made to determine whether or not the effectiveness of the ovarian follicular hormone varies with the age of the rats and whether or not the dosage to be used should vary directly as the body weight of the rats.

Throughout the experiment a single preparation has been used and it apparently did not deteriorate during the period. It was put into ampoules and sterilized in the autoclave. The solution was diluted with seven parts of water just before being used. Dosages are expressed in terms of cubic centimeters of the preparation before dilution.

Column 7 gives the number of *rats per cc.* In computing these values the weight of the rats is not taken into account.

Only the value for the smallest effective dose for each individual rat is given.

These values are obtained by using the formula:

$$Rats \text{ per cc.} = \frac{1}{Q}$$

Q represents the minimum number of cc. of follicular fluid extract which will cause typical oestrus in the rat.

Column 8 gives the number of *rat units per cc.* based on the 140 gram rat as the standard. This assumes that the effective dose should vary directly as the body weight. These values are computed by the use of the following formula:

$$Rat \text{ units per cc.} = \frac{1}{\frac{140}{Q} \times \frac{W}{W}} = \frac{1}{Q} \times \frac{W}{140} = \frac{W}{140Q}$$

W represents the weight of the rat in grams. Q represents the minimal number of cubic centimeters of follicular fluid extract which will cause typical oestrus in the rat.

TABLE I  
*Rats Two to Three Months Old*

RAT	DATE	WEIGHT	DOSE CC.	CC. PER KG.	RESULT	RATS PER CC.	UNITS PFR CC.
226	Feb. 9						
	15	112	3	2.68	Typical oestrus.		
	23	126	175	1.39	Typical oestrus.		
	Mar. 3	142	25	1.76	Typical oestrus.		
229	9	150	15	1.00	Typical oestrus.		
	Feb. 9						
	15	134	25	1.87	Atypical.		
	23	150	2	1.33	Typical.		
230	Mar. 3	162	225	1.39	Typical.		
	9	168	15	.89	Atypical.		
	Feb. 9						
	15	128	2	1.56	Atypical (almost no effect).		
231	23	146	225	1.54	Typical.		
	Mar. 3	158	2	1.27	Typical. . .		
	9	168	15	.89	Atypical.		
	Feb. 9						
232	15	118	.15	1.27	No effect		
	23	128	25	1.95	Typical.		
	Mar. 3	142	175	1.23	Typical.		
	9	146	15	1.03	Typical.		
	Feb. 9						
	15	102	1	.98	No effect		
	23	110	3	2.72	Typical..		
	Mar. 3	118	15	1.27	Typical.		
	9	120	125	1.04	Typical (Short)		
Optimum			125	1.00			
						8.00	7.15

*Rats Three to Four Months Old*

RAT	DATE	WEIGHT	DOSE CC.	CC. PER KG.	RESULT	RATS PER CC.	UNITS PER CC.
251	Feb. 9	140	.1	.72	No effect.....	4.45	5.65
	15	144	.2	1.39	No effect.....		
	23	162	.175	1.08	Typical?.....		
	Mar. 3	172	.25	1.45	Typical.....		
	9	178	.225	1.26	Typical.....		
252	Feb. 9	148	.2	1.35	Typical.....	5.72	7.5
	15	142	.175	1.23	No effect.....		
	23	162	.2	1.23	Typical.....		
	Mar. 3	172	.225	1.30	Typical.....		
	9	184	.175	.95	Typical.....		
253	Feb. 9	144	.3	2.08	Typical.....	5.72	7.5
	15	150	.15	1.00	No effect.....		
	23	166	.225	1.35	Typical.....		
	Mar. 3	176	.2	1.14	Typical (Short).....		
	9	184	.175	.95	Typical.....		
255	Feb. 9	152	.4	2.63	Typical.....	5.00	7.06
	15	160	.125	.78	No effect.....		
	23	182	.25	1.37	Typical.....		
	Mar. 3	192	.175	.91	Atypical.....		
	9	202	.20	.99	Typical.....		
259	Feb. 9	130	.5	3.85	Typical.....	5.00	5.65
	15	130	.1	.77	No effect.....		
	23	146	.3	2.05	Typical.....		
	Mar. 3	158	.20	1.27	Typical.....		
	9	158	.20	1.27	Typical.....		
Optimum			.175	.95		5.72	7.5

*Rats Seven to Eight Months Old*

RAT	DATE	WEIGHT	DOSE CC.	CC. PER KG.	RESULT	RATS PER CC.	UNITS PER CC.
174	Feb. 9	232	.20	.86	Typical.....	5.00	8.30
	15	236	.175	.74	No effect.....		
	23	236	.175	.74	Atypical.....		
	Mar. 3	208	.25	1.2	Typical.....		
	9	206	.20	.97	Typical.....		
175	Feb. 9	234	.3	1.28	Typical.....	4.45	7.30
	15	232	.150	.65	No effect.....		
	23	226	.2	.89	Atypical.....		
	Mar. 3	230	.225	.97	Typical.....		
	9	234	.20	.86	Typical? (Short).....		
176	Feb. 9	...	...	...	...	5.00	5.65
	15	...	...	...	...		
	23	...	...	...	...		
	Mar. 3	158	.2	1.27	Typical.....		
	9	...	...	...	...		
178	Feb. 9	194	.4	2.06	Typical.....	5.00	5.57
	15	190	.125	.66	No effect.....		
	23	168	.225	1.34	Typical.....		
	Mar. 3	228?	.175	.77	Atypical.....		
	9	156	.2	1.28	Typical.....		
180	Feb. 9	220	.5	2.27	Typical.....	5.00	8.22
	15	222	.10	.45	No effect.....		
	23	218	.25	1.15	Typical.....		
	Mar. 3	230	.20	.87	Typical.....		
	9	...	...	...	...		
Optimum			.20	.86		5.00	8.30

*Rats Nine to Ten Months Old*

RAT	DATE	WEIGHT	DOSE CC	CC PER KG.	RESULT	RATS PER CC.	UNITS PER CC.
141	Feb 9	234	2	.86	Typical	5 00	8 35
	15	230	2	.87	Atypical		
	23	232	175	.75	Atypical		
	Mar. 3	9	242	25	1.03		
145	9				Atypical		
	Feb 9	220	3	1.36	Typical	4 00	6.46
	15	210	175	.84	No effect		
	23	226	2	.89	Atypical		
	Mar. 3	216	3	1.39	Typical		
146	9	226	25	1.11	Typical	3 33	6 30
	Feb 9	236	4	1.69	Typical		
	15	240	15	.63	No effect		
	23	244	225	.92	Atypical		
	Mar. 3	256	275	1.07	Atypical		
147	9	264	3	1.13	Typical	3 33	6 52
	Feb 9						
	15	274	125	.46	No effect		
	23	276	25	.91	Atypical		
	Mar. 3	278	25	.90	Atypical		
148	9	278	3	1.09	Typical	4 00	8 23
	Feb 9	276	5	1.81	Typical		
	15	274	1	.37	No effect		
	23	280	3	1.07	Typical		
	Mar. 3	282	2	.71	Almost no effect		
	9	288	25	.87	Typical (Short)		
Optimum			2	.86		5 00	8 35

*Rats Eleven to Twelve Months Old*

RAT	DATE	WEIGHT	DOSE CC	CC. PER KG.	RESULT	RATS PER CC.	UNITS PER CC.
106	Feb 9	220	1	4.55	Typical	1 67	2.76
	15	226	2	.89	Atypical (almost no effect).		
	23	230	3	1.30	Atypical		
	Mar. 3	236	4	1.70	Atypical		
120	9	232	6	2.58	Typical . . .		
	Feb 9	240	8	3.33	Typical	3 33	5.52
	15	232	3	1.29	Typical (Short).		
	23	222	4	1.8	Typical. . .		
	Mar. 3	220	25	1.13	Atypical		
121	9	226	275	1.22	Atypical (typical?)		
	Feb 9	240	6	2.50	Typical	3 33	5.23
	15	228	4	1.75	Typical		
	23	222	35	1.58	Typical		
	Mar. 3	220	3	1.36	Typical		
126	9	222	25	1.12	Typical ? (Short)		
	Feb 9	266	4	1.50	Typical (Short)	3 33	6.39
	15	268	5	1.85	Typical		
	23	266	2	.75	Atypical (almost no effect).		
	Mar. 3	268	35	1.30	Typical (Short)		
	9	268	3	1.12	Typical .		
Optimum			3	1.12		3 33	6.39

*Table II.* Shows the values in the various age groups for the number of *Rats per CC.* of follicular fluid extract. These are the values which would be used in stating the strength of an extract if the weight of the rat were not taken into account. The deviation from the mean is given for each age group.

TABLE II

*Based on Rats Regardless of Weight.  
Arranged According to Age Groups.*

AGE*	AGE	AGE	AGE	AGE	MEAN
2-3	3-4	7-8	9-10	11-12	
<b>Optimum value</b>					
<i>rats per cc....</i>	8.00	5.72	5.00	5.00	5.41
<b>Deviation from</b>					
<i>the mean ...</i>	48.0%	5.7%	7.6%	7.6%	39.5%

*Table III* shows the values obtained in each age group for the number of Allen and Doisy *Rat Units per CC.* of follicular fluid extract. These values are based on the 140 gram rat as the standard. The deviation from the mean is also shown.

TABLE III

*Based on the 140 Gram Rat as the Standard.  
Arranged According to Age Groups.*

AGE	AGE	AGE	AGE	AGE	MEAN
2-3	3-4	7-8	9-10	11-12	
<b>Optimum value</b>					
<i>rat units per cc.</i>	7.15	7.50	8.30	8.35	7.54
<b>Deviation from</b>					
<i>the mean.....</i>	5.2%	0.5%	10.1%	10.7%	15.3%

By examination of Table II it will be noted that when the weight of the rat is not taken into account there is a wide variation in the results of tests for potency of follicular fluid. The age group 2-3 months shows a variation from the mean of 48.0 per cent, and the age group 11-12 months shows a variation of 39.5 per cent. When the weight of the rat is taken into account, as is done in Table III, the variation from the mean is only 5.2 per cent in the 2-3 months age group and 15.3 per cent in the 11-12 months age group. In the other three age groups the variation is not great in either table and the reason for this is

\* Age in months.

undoubtedly that the rats in these three groups are of nearly the same weight.

This experiment leads us to conclude that the effective dosage of follicular fluid extract varies directly as the weight of the rat. The experiment also shows that rats may be used regardless of age if they are in the prime of life. This statement must be qualified, however, by stating that only rats in which the oestrous cycles are regular with the four to six-day rhythm, before ovarieotomy, should be considered to be in the prime of life. This qualification rules out many rats younger than three months, for usually the oestrous cycles have not become regular until three months of age. The young rats used in this experiment were probably better than average in sexual development. They were selected from a group of 24 rats of the same age because they were the first to show opening of the vaginas. This experiment as well as some of our other work indicates that after 11 to 12 months of age the rat is no longer in the prime of life and should not be used for standardization of follicular fluid. As a general statement it may be said that rats between the ages of three and eleven months are the best for standardization.

In order to express the potency of our extracts of follicular fluid in terms of the Allen and Doisy *rat unit*, which is based on a rather small rat of 140 grams weight, it is necessary to take the weight of the rat into account and to use the factor, weight of the rat divided by 140 grams.

It is a pleasure to express our gratitude to Dr. E. M. Houghton, Director of the Medical Research Laboratories, whose interest in this problem has enabled us to carry out this work.

#### SUMMARY

1. The results are shown in an experiment on 24 rats in a period of five weeks, to determine whether or not the effectiveness of injections of extract of follicular fluid varies with the age of a rat and with its body weight.

2. The experiment indicates that the dosage of extract of follicular fluid should vary directly as the weight of the rat.

3. The age of the rat is of importance only to the extent that it should have reached sexual maturity and should not have passed the prime of life.

4. For standardization of extract of follicular fluid the best rats are those between three and eleven months of age and whose oestrous cycles are regular with the four to six-day rhythm, before ovariectomy.

5. In order to have a uniform standard we have adopted the Allen and Doisy *rat unit*.

6. Potency of preparations is computed in terms of the Allen and Doisy *rat unit* by using the factor: weight of the rat divided by 140 grams.

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# THE EFFECT OF PITUITARY PREPARATIONS ON THE BLOOD SUGAR CURVE AND BASAL METABOLISM

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In a study of the possible effects of pituitary substances on metabolism we have previously considered the nitrogen metabolism (1). The present study is devoted to possible effects on the carbohydrate and basal metabolism.

For measurement of the carbohydrate metabolism we have used the blood sugar curve of Janney and Isaacson (2). Blood sugar determinations were made by the method of Folin and Wu. While this method of study of the carbohydrate metabolism has been criticized by various observers, we can at least get some information from this method if changes are consistently produced.

Basal metabolism determinations were made with the Roth modification of the Benedict portable apparatus for the determination of oxygen consumption. The results are expressed in per cent of normal according to the Dubois scale.

The patients used were partly obese and partly of normal stature. Some of these patients were suffering from probable endocrinopathies. The details of stature as far as they concern this work are given in the accompanying table, were under standard hospital regime. No effort was made to restrict or modify the diet. The patients were not confined to bed.

Products of Armour & Company bought in open market were used. They are designated as follows: Anterior Pituitary, Posterior Pituitary, Whole Pituitary and Pituitrin. The first three are desiccated powders, the last a fluid in ampoules.

It is to be noted that there is a predominance of minus values in these patients, and under these conditions certain changes seem to be fairly constant. It has been previously noted (3) that patients suffering from mental disorders tend to have low basal metabolic rates without evidence of myxedema or hypothyroidism. In the five experiments with anterior pituitary one showed no change in metabolic rate, three showed a

Table Showing Blood Sugar and Basal Metabolism Before and After Pituitary Administration.

Case No.	Age	Sex	Weight	Height	Blood Sugar Curve			Drug and Dosage Per Diem			Blood Sugar Curve			Basal Metabolic Rate	
					Lbs.	In.	Fasting	1st Hour	2nd Hour	3rd Hour	Fasting	1st Hour	2nd Hour	3rd Hour	
6	14	M	198	64	99	136	100	114	-6	Anr. Prr. Grs. j for 30 days.....	96	126	101	112	-1
7	26	F	154	61	...	...	...	...	-1	Grs. v for 10 days; grs. xv for 16 days.....	...	...	...	...	+10
8	34	F	205	65	130	200	183	167	-5	Grs. x for 3 days; grs. xx for 10 days.....	139	188	126	135	-5
9	21	F	140	66	130	168	72	94	-18	Grs. ii for 18 days.....	73	100	80	75	-6
5	10	F	96	48	106	98	119	139	-21	Grs. i for 4 days.....	...	...	...	...	-31
5	10	F	96	48	...	...	...	...	-21	Psr. Prr. Grs. ii for 12 days.....	...	...	...	...	-27
9	21	F	140	66	130	168	72	94	-18	Grs. ii for 12 days.....	125	71	87	99	-16
1	19	M	158	69	95	93	95	107	-8	Whole Prr. Grs. x for 7 days; grs. xx for 10 days.....	97	98	101	125	100
2	43	F	142	62	...	...	...	...	-25	Grs. v i. d. for 16 days; grs. x for 14 days.....	...	...	...	...	-23
3	20	F	229	73	100	134	140	114	-12	Grs. xx for 10 days.....	103	116	153	131	-8
4	18	F	175	63	115	122	133	132	+15	Grs. xx for 11 days.....	101	138	117	122	-3
5	10	F	96	48	...	...	...	...	+2	Grs. xx for 10 days.....	...	...	...	...	-18
5	10	F	96	48	...	...	...	...	-21	Grs. xv for 14 days.....	93	100	69	91	-6
15	17	F	133	62	105	78	73	97	-11	Grs. xv for 31 days.....	...	...	...	...	+11
17	50	F	254	61	...	...	...	...	+12	Grs. xxv for 7 days.....	...	...	...	...	
9	21	F	140	66	130	168	72	94	-18	Proterin (Sora) 1 cc. intranasally by tampon for 12 days.....	107	91	91	79	-15
9	21	F	140	66	111	87	79	98	-17	2 cc. for 5 days.....	92	95	60	59	?
6	14	M	198	64	99	136	100	114	-6	2 cc. for 6 days (1 cc. $\frac{1}{2}$ hour before test).....	100	69	90	80	-6
6	14	M	198	64	74	140	108	91	-6	2 cc. for 6 days (1 cc. $\frac{1}{2}$ hour before test).....	100	126	133	86	+10
6	14	M	198	64	74	140	108	91	-6	2 cc. for 4 days (1 cc. $\frac{1}{2}$ hour before test).....	92	99	161	129	+12
											102	151	112	107	-3

definite rise in rate, and one showed a lowering. Whole pituitary showed in five out of seven experiments a slight rise of rate. Pituitrin showed in every one of four experiments a rise in rate. It is believed by some observers that this change in metabolic rate after the injection of pituitrin, though small in amount, is dependent on the integrity of the thyroid (4).

In so far as they go these experiments confirm the previous ones in regard to a slight rise in basal metabolic rate after the administration of pituitary preparations. We were unable to get any definite information about the sugar metabolism from these experiments.

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## Book Reviews

THE CHEMICAL AND PHYSIOLOGICAL PROPERTIES OF THE INTERNAL SECRETIONS. E. C. Dodds and F. Dickens · 1925. Oxford University Press, New York and London. P. 214.

The authors have assembled the data on the methods of preparation and physiological properties of the internal secretions in an excellent manner. The results of the more important investigations on insulin, tethelin, pituitrin, thyroxin, adrenaline, and the ovary are included in this text. Secretion, spermine and the parathyroids are briefly discussed. The bibliography contains many valuable references. This book is heartily recommended as an excellent treatise on the subject.

CONTRIBUTION A L'ETUDE DES DYSTROPHIES DE LA PUBERTE. G. Boulanger-Pilet, 1924. Louis Arnette, Paris.

The author offers a well written, succinct review of the literature—confined largely, however, to French writers—together with a record of a considerable number of personal clinical observations. He takes up the involvement of the skeletal structures and the adipose tissue in the pubertal dystrophies. Their origin is then discussed from both the endocrine and the nervous points of view. The work concludes with a seven page bibliography. Special importance is ascribed to the gonads among the endocrine factors and to syphilis in the genesis of disorders dependent upon nervous influences.

# Abstracts

Action of the small and large doses of adrenaline upon the motility of the small intestine of man. Danielopolu (D.), Simici (D.) & Dimitriu (C.), Compt. rend. Soc. d. Biol., 1925, 92, 1146-1148; Abst., Rev. franc. d'Endocrinology, 6, 436.

Small doses of adrenaline affect the parasympathetics exclusively while large doses have an effect predominantly upon the sympathetics. Thus small doses retard cardiac rhythm, decrease blood pressure and exaggerate gastric and oesophageal motility, while the larger doses accelerate the heart rhythm, raise the blood pressure and inhibit the stomach and oesophagus. The work of the authors shows that these conclusions are applicable also to the action of adrenaline upon the small intestine of man. An intravenous injection of 1 cc. of a 1/300,000 of adrenaline exaggerates the amplitude of the peristaltic contractions. A much larger dose produces a marked diminution of the contractions. Occasionally the peristaltic contractions disappear entirely.

Experiments with adrenal insufficiency. Hartman (F. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 467-468.

Seventeen adrenalectomized cats lived on the average about 50 hours after operation when untreated. Cats treated with injections of cortical extract, obtained with alcohol, ether, glycerol and olive oil, lived to varying periods up to 90 hours. Twenty-two cats treated with saline extracts of cortex lived on the average 146.6 hours.—J. C. D.

Action of adrenalin, pituitary extract, and histamin on capillaries of frog tongue (Untersuchungen über die Wirkung von Adrenalin, Hypophysenextrakt und Histamin auf den Blutstrom in den kleinsten Gefäßen der Froschzunge). Killian (H.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925, 108, 255-279.

Adrenalin applied directly or given subcutaneously produced contraction of arteries, arterioles and arteriole capillaries. Pituitary extract applied locally or given by subcutaneous or intravenous injection caused general vaso-constriction. Histamin brought about general vaso-dilatation extending to the venous capillaries. Effects were recorded photographically.—G. E. B.

Histological changes in the adrenal glands of guinea pigs subjected to scurvy and severe inanition. Medes (Grace) & Lindsay (Blanche), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 393-394.

These glands show hemorrhagic infiltration between the columns of cortical cells at the periphery of the medulla. There is also cell degeneration but this is not so striking. These changes agree with those described by McCarrison in 1921 in similar experiments.

**The action of adrenine on the nitrogen, creatinine, and creatine excretion** (Zur Frage der Wirkung des Adrenalin auf die Stickstoff-, Kreatinin- und Kreatinausscheidung). Palladin (A.) & Tichwinskaja (W.), Arch. f. d. ges. Physiol. (Berl.), 1925, 210, 436-441.

If adrenine is injected once daily in gradually increasing doses into rabbits, it has no influence on nitrogen or creatinine excretion with normal diet. If it is injected twice daily, with rapidly increasing doses, there is on the other hand markedly increased excretion of nitrogen and creatinine, and further, creatinuria.—A.T.C.

**Tolerance for epinephrine.** Ricaldoni (A.), Bull. Soc. Méd. d. hôp. (Par.), 1925, 49, 1627-1628; Abst., J. Am. M. Ass., 86, 724.

Ricaldoni examined a patient with asthma who had been in the habit of injecting himself with epinephrine for 13 years (0.006 gm. daily for 10 years, then from 0.009 to 0.012 gm. daily for 3 years). This epinephrine addiction did not seem to have induced marked changes in the cardiovascular apparatus. The man was thin and pale, but his earning capacity was unimpaired and there was no hypertension.

**Addison's disease, with report of cases.** Swan (W. H.) & Bortree (L. W.), Boston M. & S. J., 1926, 194, 712-714.

A brief consideration of seven patients, all of whom had tuberculous histories. All patients died. Substitution therapy of various kinds was tried in six cases. In one case pituitary extract relieved the patient somewhat, but in the other cases no result could be observed.—J. C. D.

**The blood sugar level and the epinephrin content of the suprarenals of the rabbit in diphtheritic intoxication.** Mikami (S.), Tohoku J. Exper. Med. (Sendai), 1925, 6, 299-324.

Diphtheria toxin (0.1 cc.) was injected intravenously into rabbits (0.5-5.5 cc. per kgm.). The lethal dose for the guinea pig is 0.12 cc. In doses above 3 cc. the blood sugar increased 81% or more, reaching its maximum in 2 to .5 hours. In smaller doses 0.8-3 cc. diluted with saline (0.024-0.2 kgm.) hyperglycemia, averaging 133%, occurred in 2 to 6 hours. Rabbits died in 24 hours. The upper limit of original toxin fluid not capable of calling forth hyperglycemia was 0.05 cc. per kgm. In one series where 0.02-0.05 cc. per kgm. was used, rabbits were killed 24-29

hours later. Blood sugar was low, liver glycogen and epinephrin of adrenals low as well. As a control, rabbits were injected with the same quantity of bouillon fluid with negative results. As a second control the toxin was neutralized by antitoxin and the same quantity injected with negative results. Double splanchnectomy prevented any marked rise of the diphtheria hyperglycemia. The author explains diphtheria hyperglycemia as being of central origin. He further studied the epinephrin content of the adrenals hourly in the course of diphtheria poisoning, which brought on depletion of the epinephrin storage of the adrenals. The loss was small the first hour, reached its peak about the sixth hour, decreased again so that it reached its normal at about the eighth or ninth hour of the poisoning. As the blood sugar went up, the epinephrin content of the adrenals went down, the hyperglycemia curve slightly preceding; finally both curves came together in the ninth and tenth hour. Toward the end of life, blood sugar content and epinephrin store were greatly decreased, liver glycogen remaining the same. In one group of rabbits the splanchnic nerves on one side were previously divided; one-half of these were killed at the sixth hour, the other half at the twenty-first and thirty-sixth hour of intoxication. In the first group the epinephrin of the intact side was greatly decreased and on the denervated side almost unchanged. In the second series the absolute quantity and percentage content of epinephrin was the same in both glands. In such a long period of poisoning, denervation could not protect the gland from loss of epinephrin. In the dying period of poisoning about 2/5 of the epinephrin storage was gone. When an animal is gradually poisoned with diphtheria toxin and lives a day or more in a somewhat moribund state, not hyperglycemia but hypoglycemia occurs. This persists 24 hours or more. The epinephrin of the adrenals as well as liver glycogen are markedly diminished. Double splanchnectomy does not protect the animal from the diminution of these 3 substances.—H. J. John.

**The ovarian follicular hormone: a study of variation in pig, cow and human ovaries.** Allen (E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 383-387.

The author used as a standard for comparing the potency of different samples of follicular hormone the least amount of lipid extract that will produce a definite physiological reaction in the spayed adult rat. Using this standard he finds in sows a variation from 28 rat units before ovulation to 2.1 units after ovulation, and in cows from 4.6 units before to a non-measurable amount after. In the human the highest value, 7 rat units, was during the third week from the start of the previous menstruation. In the fourth week the yield was 2 units. In women, then, the hormone content is high and it does not vary as abruptly as in cows and sows.

"This might account in part for (1) the longer duration of the menstrual cycle (in man), (2) the longer portion of the cycle during which mating instincts may be in evidence, and (3) the continuance of the anabolic and secretory phase for a considerable period after ovulation."—J. C. D.

**The menstrual cycle in the monkey; effect of double ovariectomy and injury to large follicles.** Allen (E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 434-436.

The work was carried on with five monkeys. The author summarizes and concludes: (1) The removal of both ovaries on the first day of menstruation had no apparent effect on that period. (2) Double ovariectomy or injury to large follicles dated toward the end of, or immediately after, the follicular phase of the cycle was followed by apparently typical menstrual bleeding. These experimental menses appeared from 5 to 13 days before the expectation as calculated by the length of previously observed cycles and by Corner's mode for cycle length to 27 days. (3) External coloring and swelling disappeared after double ovariectomy. From these data it is concluded that menstruation is probably due to an absence of follicular hormonal stimulus after it has been acting for a certain period of time. In this connection it should be noted that the presence of the follicular hormone has been demonstrated in human corpora lutea. It is quite possible that the corpus of the monkey may also continue to secrete the follicular hormone, thus postponing the onset of menstruation.—J. C. B.

**Ovarian grafting.** Bell (W. B.), Surg., Gynec. & Obst. (Chicago), 1925, 41, 706-710.

Ovarian grafting rather than complete ovariectomy is recommended in certain cases of salpingo-oöphoritis and non-malignant ovarian neoplasms. In the series of cases reported upon, auto-plastic grafts alone were successful. The most desirable location was the body of the rectus muscle. Out of a total of 187 cases, 118 were analyzed. Functional results, or the non-appearance of symptoms of the menopause, were obtained in 80% or 98 of these cases. Menstruation has continued in some cases for as long as seven years after the operation. In two cases the formation of follicular cysts in the grafts was accompanied by menorrhagia.

—M. O. Lee.

**Necrosis of the corpus luteum of pregnancy.** Brennan (D.) & Cohen (M.), Surg., Gynec. & Obst. (Chicago), 1926, 42, 228-235.

This may occur in pernicious vomiting of pregnancy, and probably has the same significance as has necrosis of the liver and kidneys in this disease.—A. T. C.

The sexual cycle in the female of mammals. The follicular phase. (*Le cycle sexuel chez la femelle des mammifères. Étude de la phase folliculaire*). Courrier (R.), Arch. de biol. (Liège & Par.), 1924-25, 34, 369-473; Abst., Physiol. Abst., 1926, 10, 605.

In the adult female of mammals the generative organs and mammary gland undergo cyclic changes which are chronologically and intimately connected with the maturation of the Graafian follicles and the formation of the corpus luteum. During the former process (follicular stage) the mammary and uterine glands become hypertrophic, the oviduct enters a phase of intense secretion, and the vaginal epithelium actively proliferates. These phenomena are considerably accentuated during the luteinic stage. They are very likely brought about by a substance (folliculine) which can be extracted from the liquor folliculi and used for control experiments.

The specific dynamic action of protein in children before and during the period of puberty. Göttche (O.), Klin. Wchnschr. (Berl.), 1925, 4, 2062-2064; Abst., Chem. Abst., 20, 228.

The sexual hormone and the thyroid hormone increase the basal metabolic rate and decrease the specific dynamic action of protein. The action of the hypophyseal hormone is the reverse of the above. In short, the hypophysis is antagonistic to the thyroid and to the sex glands. Ingestion of protein by adults increases the oxidation process by 30%. In young children (pre-puberty period) protein calls forth only a 20% increase in the oxidation rate. In such children the hypophysis and thyroid are active; but the sexual hormone is absent. The action of the hypophysis is predominant. The early stages of puberty are characterized by a 10-35% increase in the basal metabolic rate and a marked decrease in the specific dynamic action of protein, the mean value being about 5% as compared to 30% in adults. The influx of the new hormone has destroyed the previously existing balance between the hypophysis and thyroid with a temporary suppression of the hypophyseal activity. The period of puberty is associated with a tendency to establish a new balance between the endocrine organs so that the basal metabolic rate steadily decreases to normal and the specific dynamic action of protein steadily rises to the adult value of 30%.

The corpus luteum as the source of the follicular hormone. Johnston (C. G.) & Gould (V. L.), Surg., Gynec. & Obst. (Chicago), 1926, 42, 236-240.

The amount of care exercised in collecting corpus luteum material is an important factor in testing for the follicular secretion. Using rats and rabbits, no noticeable changes were produced in the genital tract by injection of the alcohol-ether-acetone extract of carefully collected corpora lutea of pigs. Neither pregnancy, nor

the size, consistency, nor color of the corpora lutea had any effect on the results obtained, while repeated positive results have been obtained with the corresponding extract of the liquor folliculi of hog ovaries. It is concluded that the corpus luteum does not produce the active internal secretion which produces hyperplasia of the uterus and vagina.—A. T. C.

**Estrus-inducing hormone.** Lacquer (E.), Hart (C. P.), de Jongh (S. E.) & Wijsenbeek, Deutsche med. Wchnschr. (Berl.), 1926, 52, 52-54; Abst., J. Am. M. Ass., 86, 727.

The authors confirm Zondek and Brahn's discovery of a water soluble hormone of the estrual cycle. They suggest the name "menformon" for it, but want it reserved exclusively for such preparations as contain in 1 mgm. of substance at least ten doses sufficient to provoke the estrual cycle in a castrated mouse. The pure preparations contained too little substance to be analyzed chemically. They believe that the hormone probably contains no protein nitrogen, phosphorus or cholesterol.

**The use of corpus luteum to prevent nausea in radiation therapy of uterine conditions.** Lafferty (R. H.) & Phillips (C. C.), Am. J. Roentgenol. & Therapy (N. Y.), 1925, 14, 381-486.

The patients in the 16 cases reported ranged in age from 25 to 45 years. Of these, 10 were entirely relieved, 4 were improved and 2 were unimproved. One of the unimproved patients was 25 years of age, the other 45. All of these 16 patients were known to become very much nauseated following small doses of roentgen rays, when corpus luteum was not used. Some of those listed as completely relieved were given the extract on alternate treatments and each time it was not given they were very much nauseated. In making this report the authors assert that they realize that the number of cases is too small to warrant positive conclusions, but the results were so uniformly good that it seemed wise to report them in order that others may try the same treatment. It is important, in their opinion, that the injections be given intravenously, 1 to 2 cc. being used immediately after radiation treatment.

—Author's Abstract.

**Ovarian Grafts.** Pettinari (V.), Arch. Ital. de Biol. (Pavia), 1924, 74, 62-72.

Pettinari has made a large number of grafts of ovaries in several species of animals. He reports the expected signs of secretion of grafts and correlates these results with a histologic study. Follicular maturation with corpus luteum formation may occur in autoplastic grafts: follicular atresia is characteristic of heterosexual grafts. He concludes that the follicles are the principal source of hormone production, the corpus luteum having no par-

ticular endocrine action. He believes that the hormone from the follicles is the only one necessary for hypertrophy and secretion of the mammary glands.—E. Allen.

**Fate of ovarian graft.** Rheaume (P. Z.), Union méd du Canada (Montréal), 1925, 54, 686-690; Abst., J. Am. M. Ass., 86, 518.

Rheaume had opportunity to examine an ovary that had been transplanted into the abdomen after bilateral ovariectomy five years before. After the operation the woman suffered exceptionally severely from the phenomena of the induced menopause. At the recent laparotomy (required for a different disease) the ovary appeared reduced to one-half its former size. It was enclosed in a fibrous capsule but was abundantly supplied with vessels and was well nourished and anatomically almost intact. The physiologic function of the gland, however, had evidently never been resumed. Rheaume thinks that ovarian grafting is worth even less than grafting monkey testicles in men.

**Experimental hyperthyroidism and the germ glands in amphibians, with special reference to the primitive interstitial tissue.** Speidel (C. C.), Anat. Record (Phila.), 1925, 31, 65-78.

Frog tadpoles, in which metamorphosis has been hastened by desiccated sheep thyroid, exhibit an increase in the mitotic activity of the intertubular mesenchymal cells. These cells are held to be the progenitors of the interstitial cells. Thyroid treated tadpoles also show a definite, though not conspicuous, increase in the rate of proliferation of spermatogonia and, to a lesser degree, oögonia. The author believes that the effect of hyperthyroidism upon the primitive interstitial cells suggests a part of the mechanism by which early maturity in secondary sexual characteristics is attained by hyperthyroid individuals.—W. J. A.

**Release of the sexual cycle, development of the sex characteristics, reactivating action on the senile female organism through ovarian and placental extract (Auslösung des sexualzyklus, Entwicklung der Geschlechtsmerkmale, reaktivierende Wirkung auf den senilen weiblichen Organismus durch Ovar- und Placentaextrakt).** Steinach (E.), Heinlein (H.) & Wiesner (B. P.), Arch. f. d. ges. Physiol. (Berl.), 1925, 210, 598-611.

The experiments reported were made with rats and guinea pigs, the results of which are indicated in the title.—A. T. C.

**Rejuvenation.** Walker, K. M., Practitioner (Lond.), 1925, 115, 84-90.

This is a general discussion without experiments or detailed case reports. The author has seen some improvements as a result of ligating the vas deferens, but better results from transplants of

human testicle into the tunica vaginalis. The improvement in these patients is general but not particularly noticeable in the realm of sexual functions. He finds ligation of the vas specially beneficial in paralysis agitans.—J. C. D.

**Aqueous solution of ovarian hormone.** Zondek (B.) & Brahn (B.), *Klin. Wchnschr. (Berl.)*, 1925, 4, 2445-2446.

A method described in abstract for the preparation of a water soluble extract of placenta or ovarian follicular fluid. The lipoid residues from alcohol, ether and chloroform extractions were boiled in acetic acid. The filtrate was cooled, causing a precipitate to settle out. This was then cleared and neutralized. It was then concentrated in vacuo and used for injections. No statement is made of the number of tests nor the yield of active material. The extract was tested for activity by injections into spayed mice, the oestrous reaction of the vaginal epithelium being the criterion of a positive extract. Intravenous injections into mice and guinea pigs were not injurious.—E. Allen.

**The hypophyseal cachexia—A synthetic review (La chasessia ipofisaria—Rivista sintetica).** Bolsi (D.), (Siena), 1924, S. Bernardino.

The syndrome discovered by Simmonds (1914) is more characteristic in women than in men, owing to the partial and finally the total disappearance of menstruation before the climacterium. Other symptoms in progressive cachexia are: loss of weight, modification of the skin (which becomes light yellow), early senility, loss of body hair—very seldom the head hair, loss of teeth (partial or total), sometimes atrophy of the lower jaw, a severe degree of anemia, sometimes eosinophilia and at times hypothermia. In the nervous system one finds asthenia and adynamia and even apathy and psychomotor torpor. The syndrome is hardly ever complete. In a case of quick growing tumor the hair symptoms as well as the cachexia may not show. At times there is no note of senility. Fever occurs only in cases of septicemia. Polydipsia and polyuria and even acromegalic symptoms may appear, preceding the cachexia. A case reported by Mieremer showed only a condition of lethargy and lesion of the hypophysis. In a rapidly growing tumor the process may be very quick, but usually is very slow. Arrest of symptoms is seldom found. Hypophyseal ophotherapy seems to be of some value though never entirely curative. The syndrome is oftener found in women and it might be referred to embolism (often after confinement) with consequent fibrosis of the gland (Simmonds). Fahr contends instead for an inflammatory process. Lesions of other glands have often been found, especially the thyroid, the adrenals and the ovaries.—G. Vercellini.

**A case of sclerosis of the anterior lobe of the hypophysis with cachexia (Un caso di sclerosi del lobo anteriore dell' ipofisi—considerazioni sulla cachexia ipofisaria.)** Bolsi (D.), (Siena), 1925, S. Bernardino.

A case of cachexia in a woman who had dementia praecox from the age of 20 years and a torpid tuberculous lesion at the apex of her right lung diagnosed at her 55th year. At autopsy the anterior lobe of the hypophysis appeared very much reduced, leaving an empty space in the sella. The posterior lobe appeared normal, but there was sclerosis of the pars intermedia and even more of the anterior lobe. The total weight of the gland was 32 cgm. Discarding the mental condition as well as the torpid tuberculous lesion as a cause of cachexia, the condition would appear to have been due to the hypophyseal lesion.—G. Vercellini.

**Late eunucoidism and syphilitic dyspituitarism (Eunucoidismo tardivo e dispituitarismo sifilitico).** Coppola (A.), (Siena), 1925, S. Bernardino.

The patient reported by the author was of a family in which polysarcia and familial deafness were found in the last four generations. The patient contracted syphilis when 28 years of age. He was under treatment only three months. He was married at the age of 30 and had five children, three of whom were living. From the ages of 28 to 30 he gained 20 kgm. in weight. At 48, following a severe fronto-occipital headache (four months) he lost 34 kgm. in weight, 25 teeth were lost in a few weeks and he had severe polyuria and polydipsia (two months). He improved on mercurial treatment, but two years after had a gummatous osteitis of the nasal bones, which improved under new mercurial treatment. At 50 he lost his potentia and three years later his voice had lost its male timbre, and all the hair of the body (head excepted) had fallen. Finally he presented asthenia and hypersomnia. The x-ray showed diffused basilar hyperostosis. The pluriglandular syndrome can be explained by the action of the hypophysis on the gonads and of these on the thyroid as well as on the adrenals.

—G. Vercellini.

**Relation of the pituitary to carbohydrate metabolism (Zur Frage einer Beziehung der Hypophyse zum Kohlenhydratstoffwechsel).** Fukui (T.), Arch. f. d. ges. Physiol. (Berl.), 1925, 210, 427-431.

Injection of posterior and of anterior pituitary extracts had no definite influence on the liver glycogen of normally fed rats, and did not influence the effect of thyroid on liver glycogen.—A. T. C.

**Mid-brain changes in diabetes insipidus (Ueber Zwischenhirnveränderungen bei Diabetes insipidus).** Kiyono (H.), Arch. f. path. Anat. u. Physiol. (Berl.), 1925, 257, 477-489.

Report of the case of a 59-year-old woman who had shown symptoms of diabetes insipidus for 13 years. Her father died of diabetes, her mother of carcinoma of the uterus. Another member of her family had Addison's disease. The outstanding symptoms in this case were thirst, polyuria, intestinal disturbances, gradually increasing weakness, staggering gait, partial deafness. The anatomical basis for the diabetes insipidus was found in a marked round cell infiltration of the tuber cinereum. The cell nuclei in the tuber cinereum, nucleus tuberis, nucleus supraopticus and the nucleus paraventricularis were markedly changed. There was pronounced atrophy of the posterior lobe of the hypophysis, which the author believed to be a result of the long continued intense injury to the tuber cinereum. The thyroid showed atrophy of the acinar epithelium and marked fibrosis. Other glands of internal secretion also showed pathological changes. Chronic interstitial nephritis was present. The author believes that his findings justify the conclusion that nerve fibers pass from the tuber cinereum peripherally to the hypophysis.—J. P. S.

**A simple method for the biological assay of hypophysis preparation.**

Loewe (S.) & Ilison (M.), Klin. Wchnschr. (Berl.), 1925, 4, 1692; Abst., Chem. Abst., 20, 448.

Small pieces of frog skin, immersed in a nutrient medium, react toward hypophysis extract exactly as does the intact frog; the skin becomes deeply pigmented. Examination of such skin sections under the microscope shows that this coloration is caused by an excitation of the dormant pigment cells with a consequent pigmentation. A maximum conversion of dormant into active pigment cells occurs in 15 minutes. The percent conversion of dormant into active, fully pigmented cells, in 15 minutes is directly proportional to the strength of the preparation. A good preparation gives 100% conversion. This method of assay is preferable to the uterus contraction method because the reaction is specific for hypophyseal extract.

**The presence of an oxytocic substance (posterior hypophysis extract) in cerebrospinal fluid.** Shapiro (S.), Arch. Neur. & Psychiatry (Chicago), 1926, 15, 331-340.

Of 28 cerebrospinal fluids obtained from 25 different patients, none caused an oxytocic effect on the virgin guinea-pig uterus. They had, indeed, a tendency to inhibit contraction. The intravenous injection of pituitary extract failed to cause an increased secretion of the active principle present in the posterior lobe of the hypophysis into the cerebrospinal fluid within three minutes after injection.—R. G. H.

**Hypophysial fat dystrophy with hyperglycemia and glycosuria.**  
Shapiro (S.) & Kliatsheo (M. G.), Arch. Neurol. & Psychiat. (Chicago), 1926, 15, 85.

The patient was a woman 47 years of age with typical hypophysial fat dystrophy associated with a tumor in the region of the hypophysis. This was definitely proved by roentgen and careful neurological examinations. In addition hyperglycemia and glycosuria were present. It is the general belief that the fat dystrophy which occurs in Fröhlich's syndrome results from increased fat formation consequent to the high glucose tolerance that usually is seen in these cases. The development of increased fat deposits in the presence of an apparent diabetes mellitus, therefore, is offered as evidence that the fat dystrophy is not dependent upon an increased glucose tolerance for its formation.—Authors' Abstract.

**The chemical regulation of the heart beat by the liver (Ueber die chemische Regulierung des Herzschlags durch die Leber).** Asher (L.), Arch. f. d. ges. Physiol. (Berl.), 1925, 209, 605-606.

When all sources of error are excluded, the perfusate from the liver still contains a specific substance which, tested on the frog's heart, augments and accelerates the beat.—A. T. C.

**Studies on the influence of diet on the action of certain internal secretions. III. Insulin and adrenaline action with acid as compared with basic diets (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe. III. Insulin- und Adrenalinwirkung bei Verabreichung "saurer" bzw. "basischer" Nahrung).** Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, 205, 559-570.

Rabbits on acid diet (oats) react to insulin much more weakly, as measured by lowering of blood sugar, than others on basic (green food) diet, but adrenaline produces a much stronger hyperglycemia in the former. The alkali-reserve is lowered in acid-diet rabbits, and the velocity of settling of the red corpuscles is much slower.—A. T. C.

**Influence of diet on the action of certain internal secretions. IV. (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe. (IV)).** Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, 206, 451-459.

Hyperglycemia produced artificially by subcutaneous injection of glucose is maximal with an acid diet and but slight with a basic diet. Fructose and galactose give the same blood sugar curves, no matter what the diet.—A. T. C.

**Diabetes and insulin.** Banting (F. G.), Can. M. Ass. J. (Montreal), 1926, 16, 221-232.

The Nobel lecture (Sept., 1925) giving the history of the discovery, the present method of preparation, and that of standardization, the present method of use of insulin in diabetes, evidence from case reports of improvement in carbohydrate tolerance under insulin treatment, and, in one case, that of a young boy, of regenerative acinar and islet changes in the pancreas after a year's insulin treatment, revealed at post-mortem examination following accidental death.—A. T. C.

**On the possible iodometric estimation of insulin.** Brand (E.) & Sandberg (Marta), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 313-316.

The authors allow an excess of iodine solution to react with insulin previously twice precipitated at the isoelectric point in the presence of a neutral buffer under standard conditions. The amount of iodine used in the precipitation of the insulin which results is estimated by titration. The results obtained by this method so far parallel very closely the values as found by the physiological method.—J. C. D.

**The relation of the thyroid gland to the action of insulin.** Burn (J. H.) & Marks (H. P.), J. Physiol. (Lond.), 1925, 60, 131-141.

The experiments were made to test further Macleod's hypothesis that during hypoglycemia produced by insulin the liver discharges glycogen and raises the blood sugar to the normal level. They find that section of both splanchnic nerves in the cat increases the hypoglycemic reaction of insulin. In rabbits when the hyperglycemic reaction to adrenalin is large, the hypoglycemic reaction to insulin is small and vice versa. Thyroidectomy diminishes the adrenalin and increases the insulin reaction. Thyroid feeding, so long as the liver glycogen is not diminished, increases the reaction to adrenalin and decreases the reaction to insulin. In prolonged thyroid feeding if the liver glycogen disappears the hyperglycemic reaction to adrenalin diminishes and the hypoglycemic reaction to insulin increases. The evidence confirms the view that the liver by liberating sugar from its glycogen store antagonizes the hypoglycemia produced by excess of insulin in the circulation.—T. C. B.

**Insulin-glucose treatment of surgical shock and non-diabetic acidosis.** Fisher (D.) & Mensing (E.), Surg., Gynec. & Obst. (Chicago), 1925, 40, 548-555.

Three cases of pre-operative, non-diabetic acidosis are reported in which subcutaneous administration of insulin, with glucose given intravenously caused a disappearance of ketosis far more rapidly than glucose alone. In five cases of surgical shock the same treat-

ment caused a rapid and definite disappearance of the typical clinical symptoms.—A. T. C.

**II. Physical and chemical studies of human blood from cases of diabetes mellitus.** Foshay (L.), Arch. Int. Med. (Chicago), 1926, 37, 18-31.

A study of the physical and chemical changes which occur in the blood of diabetic patients as a result of the anhydremic or hydremic effects of hypoglycemia. Sixty-one samples of defibrinated blood from 22 cases of diabetes mellitus were analyzed for electrical conductivity of whole blood and of blood serum, erythrocyte counts, volumes per cent of serum and cells, average erythrocyte volume, glucose and chlorin concentrations in both serum and erythrocytes, and in some cases the serum carbon dioxid combining power. In young, untreated diabetic patients without arteriosclerosis, anhydremia and diminished alkaline reserve were noted constantly, as evidenced by depression of the electrical conductivities, high erythrocyte counts, diminution in the volume per cent of serum, increase in the volume per cent of cells, diminution of whole blood chlorides, frequently an increase in the corpuscular chlorid, and a diminution of the serum carbon dioxid combining power.

In arteriosclerotic diabetic patients, hydremia was the rule. The electrical conductivities were not depressed, erythrocyte counts were normal or lower, the volume per cent of serum was higher than normal, the average erythrocyte volume was not increased, blood chlorid was not diminished, and the serum carbon dioxid combining power was within normal limits. The blood findings from all patients in diabetic coma were alike regardless of the presence or absence of arteriosclerosis, and represented merely an exaggeration of all the departures from the normal that are customarily present to a much less extent in all young diabetic patients. In young patients with diabetes there is evidence of both anhydremia and diminution of the alkaline reserve at all times, which disappear rapidly under insulin and dietetic therapy. In arteriosclerotic diabetic patients, exsiccation and anhydremia do not occur, and there is no evidence of diminished blood alkalinity until the patient is in coma or nearly so. Anhydremia itself produces acidosis and in the younger patients this is added to the volatile acidosis which results from deranged fat metabolism. Hence the young diabetic patient is always potentially a case of impending diabetic coma. Adequate therapy demands special attention to the fluid intake. The absence of anhydremia in arteriosclerotic patients is believed to be due to arteriosclerotic changes in the kidneys which do not permit the latter to respond to hyperglycemia by excessive diuresis.—Author's Abst.

The chemical nature of insulin. Funk (C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 281.

A precipitate was obtained by treating insulin containing 10 clinical units per mgm. with naphthol yellow S. This precipitate was physiologically active. Study of it indicates that insulin is probably a polypeptide with a molecular weight around 700. It contains one atom of sulphur and 20 of nitrogen.—J. C. D.

Surgical complications of diabetes under insulin treatment. Gager (L. T.), Surg. Gynec. & Obst. (Chicago), 1925, **40**, 630-634.

Use of properly balanced diet and adequate doses of insulin will maintain carbohydrate metabolism sufficient to prevent acidosis, and keep the blood sugar low, thus providing an essential basis of satisfactory wound healing. Infections should be given the benefit of early operation, both from the standpoint of the diabetes and of the surgical condition.—A. T. C.

Action of the pancreas on the vagus [Action due pancréas sur le tonus et l'excitabilité pneumogastrique (Note préliminaire.)] Garrelson (L.), Santenoise (D.) & LeGrand (A.), Compt. rend. Soc. de biol. (Par.), 1925, **93**, 1233-1235.

A preliminary report regarding the effect of the pancreas on the vagus. The removal of the pancreas causes acceleration of the heart rate and decrease of the amplitude. The respiratory rhythm is also affected. An active substance is secreted into the blood stream by the pancreas.—E. Larson.

Hypoadrenalinism and dysinsulinism. A new pluriglandular syndrome (Typo-épinéphrie et dysinsulinisme. Nouveau syndrome pluriglandulaire). Gougerot (H.) & Peyre (E.), Compt. rend. Soc. de biol. (Par.), 1925, **93**, 1202-1203.

A report of four cases in which there was a low blood sugar (60-67 mgs. per 100 cc.) associated with an abnormal fatigability and vascular hypotension. The mechanism of the condition is obscure. Three of the subjects were syphilitic. The condition was improved by antisyphilitic combined with pluriglandular treatment. It is stated to be important to recognize the relation between the adrenals and the internal secretion of the pancreas.—E. Larson.

The method of action of insulin. I. Insulin and the glucose partition between fluid and non-fluid systems (Zur Frage der Wirkungsweise des Insulines. I. Insulin und die Glucoseverteilung zwischen flüssigen und nichtflüssigen Systemen). Häusler (H.) & Loewi (O.), Arch. f. d. ges. Physiol. (Berl.), 1925, **210**, 238-279.

Glucose added to a suspension of blood-vessel pulp in normal saline, oxalate plasma or serum, remains completely in the liquid

phase. In presence of insulin, 6% of glucose on the average, is bound to the tissue. Glucose added to sodium fluoride ox blood is not bound to the corpuscles; insulin binds it. Human sodium fluoride blood partitions glucose between cells and plasma. Insulin increases the amount bound to the cells. Human red blood corpuscles saturated with glucose give up to glucose-free saline less glucose in the presence of insulin. The degree of insulin action depends on the glucose concentration of the system, the amount of insulin, the proportion of red cells and the nature of the fluid system, the effect in saline being much less than in serum or plasma, while increased concentrations of sodium fluoride inhibit the action. Such changes must be considered before direct action of glucose on carbohydrate can be held demonstrated.—A. T. C.

The method of action of insulin. II. Insulin and the phosphate and potassium content of blood (Zur Frage der Wirkungsweise des Insulins. II. Insulin und der Phosphat- und Kaliumgehalt des Blutes). Häusler (H.) & Heesch (O.), Arch. f. d ges. Physiol. (Berl.), 1925, 210, 545-549.

Blood dilution through bleeding is produced through a tissue fluid, containing less phosphate and much less potassium than blood. At the height of the action of a subcutaneous injection of insulin the phosphate and potassium content of blood is definitely lowered; this is independent of blood dilution, since it takes place in the absence of dilution. Under similar *in vitro* conditions in which insulin causes transference of glucose from fluid phase to red cells there is no action on the partition of inorganic phosphate and potassium.—A. T. C.

Embolic gangrene of the extremities in pneumonia. A report of a case occurring in diabetic coma with an observation on the sugar content of cerebrospinal fluid during insulin shock. Kiefer (E. D.), Brigham (G.) & Wheeler (R. R.), Boston M. & S. J., 1926, 194, 192-199.

The patient received 520 units of insulin in 22 hours during which his blood sugar fell from 1080.mgm. to 56 mgm. per 100 cc. Insulin shock followed and was relieved by glucose. A lumbar puncture made at the time blood sugar was minimum showed 333 mgm. of sugar per 100 cc. compared to the normal of 60 to 100 mgm. This shows that insulin shock is not due to a lack of sugar in the spinal fluid and suggests that the fall in the sugar content under insulin is slower in the spinal fluid than in the blood. The danger of very rapid appearance of coma in diabetics with infections is emphasized together with the need of heavy doses of insulin to meet such a crisis.—J. C. D.

**Diabetic and non-diabetic glycosuria in the surgical patient.** Menniger (W. C.), Surg., Gynec. & Obst. (Chicago), 1925, 41, 454-460.

In a series of 47 cases treated before insulin there were 20 deaths. In a series of 22 cases treated with insulin there was one death. Traumatic glycosuria may be effectively treated, when necessary, with insulin.—A. T. C.

**Distribution of insulin in the normal and pancreatic diabetic dog.**

Nothmann (M.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925, 108, 1-63; Abst., Chem. Abst., 20, 441.

The pancreas, liver, muscle, blood, spleen, kidney, heart, lung, thyroid, salivary gland, brain and testis of normal dogs were tested for the presence of substances which, acting like insulin, would reduce the blood sugar in rabbits. With one exception (the spleen of one dog) all organs yielded active extracts, whose effects were identical with those of insulin. In the rabbit deprived of food they caused a fall in blood sugar and the glycogen content of the liver and the musculature of normal rabbits was diminished. In animals with pancreatic diabetes the extracts reduced the blood pressure and simultaneously diminished the sugar output through the urine. Extracts prepared from the tissues of dogs with pancreatic diabetes were without insulin-like action with the exception of those prepared from liver tissue. In these animals the amount of active principle in the liver was but slightly less (4.03 units per 100 g. of fresh liver) than that of the liver of the normal animal (4.44 units). To a high degree the amount present in the liver is independent of the glycogen content of the liver and of the time after extirpation of the pancreas. Ether narcosis does not modify the content in insulin-like material. The principle derived from the liver of pancreatic diabetic dogs markedly reduces the glycogen content of liver and muscle of normal rabbits and may lead to convulsions. Injected intra-arterially it changes the blood sugar relationships in both the arterial and venous blood. Injections of the liver extract allowed dogs to live for 24 days after complete removal of the pancreas. Here, blood sugar was reduced, as was sugar excretion, but the glycogen content of the animal remained normal. Apparently the insulin-like substance of the dog with pancreatic diabetes is identical in all respects with that of normal dogs and with insulin.

**Studies on the denervated rabbit's iris (Über die Möglichkeit röntgenexperimenteller Verschiebung des physiologischen Inkretgleichgewichts zwischen Pankreas und Nebennieren und ihren Einfluss auf das vegetative System).** Risse (O.), & Poos (F.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925, 108, 121-148.

Following irradiation of the rabbit active substances are thrown

into the blood stream which can affect strikingly the denervated and completely atropinized pupil in producing both mydriasis and miosis. The mydriatic substance is probably adrenalin. The miosis, peripherally produced, is due to a hormone which in addition can break through an atropin paralysis and quickly restore sensitivity to light. It is suggested that this hormone is produced by the pancreas.—G. E. B.

A clinical and pathologic study of twenty-six cases of diabetes.  
Root (H. F.), & Shields (W.), Boston M. & S. J., 1926, 194, 45-53.

Analysis of the etiology shows obesity as a factor in all except one case. Syphilis, heredity and acute infections played an inconsistent part. One case was associated with hyperthyroidism, which had preceded the diabetes. The average duration of the disease was 9.2 years. The highest mortality was in the young and the old. The greatest danger period was during the first two years of the disease. In ten cases death probably would have been preventable with a better knowledge of the disease and its dangers. In the pathology the striking thing is the evidences of regeneration in the Islands. We have here a cycle of destruction and regeneration of active cells similar to that found among the parenchymal cells of the liver. This is strikingly shown in "bronze diabetes," where the toxic agent, hemofucsin, is attacking both liver and Island cells and where the results can be seen to be alike. The authors offer a new interpretation of the pathology of the pancreas in diabetes mellitus. The long continued action of an injurious agent (or possibly excessive functional activity) causes a gradual destruction of islands, and at times of acinar, cells. New cells are formed to take the place of those destroyed, only to be exposed to the injurious influence with consequent pathologic change. Their injury is followed by the production of more new cells. The rarity of death from uncomplicated diabetes in cases of long duration is consistent with the conception of regeneration of the Islands of Langerhans. The first two years of the disease constitute the danger zone, during which period special effort should be made to protect the patient against coma. The disturbed carbohydrate metabolism giving rise to abnormal fat or protein metabolites may be a contributing cause of the high incidence of vascular disease in diabetic patients.—J. C. D.

Use of insulin in eclampsia. Stander (H. J.) & Duncan (E. E.),  
Am. J. Obst. & Gyn. (St. Louis), 1925, 10, 823-825; Abst., J. Am.  
M. Ass., 86, 650.

The treatment of eclampsia employed by Stander and Duncan is as follows: As soon as the patient is admitted the modified Stroganoff treatment is started; a specimen of blood is obtained and a chemical analysis made immediately. The sugar and carbon

dioxide values are carefully noted, and should these show an undue rise in the blood sugar and a decrease in the carbon dioxide combining power, from 15 to 25 units of insulin is administered. Usually a protective dose of glucose, about 2 gm. per unit of insulin, is also given. With a marked hyperglycemia, it is, perhaps, not necessary to give glucose with the insulin, but in such cases it is advisable to have orange juice available should the patient develop hypoglycemia. A drop in the blood sugar level and a rise in the carbon dioxide combining power, as well as a change from coma to consciousness, usually follow the administration of insulin. The indications for the use of insulin in eclampsia are coma or semi-consciousness following a convulsion, together with a carbon dioxide combining power of 30 or below and an elevated blood sugar. The dosage of insulin is gauged by the degree of hyperglycemia and the weight of the patient.

**The use of insulin in surgery and obstetrics.** Starr (F. N. G.), & Fletcher (A. G.), Surg. Gynec. & Obst. (Chicago), 1926, 42, 194-195.

It is desirable to allow several days when possible for the determination of the severity of the diabetes and the required amount of insulin to maintain a normal blood sugar level while the patient is on a suitable diet. In emergency operations maximum amounts of insulin should be administered during the time that may be available before operation in order to reduce the blood sugar level. Thus liability to postoperative complications is reduced, especially with surgical infections such as with diabetic carbuncle, when reduction of blood sugar lessens danger of postoperative pyaemia or multiple abscess. Under insulin administration it is possible to prescribe any diet which may be considered necessary to strengthen the debilitated patient, especially in preparing for operation in chronic cardiovascular disease. Postoperatively, small doses of insulin, controlled by blood sugar determinations where possible, should be given as soon as food is taken. If marked ketosis occurs, with marked dehydration, it may be necessary to administer glucose and fluid intravenously (500 cc. of 5 per cent solution as often as required). In event of infection of severe toxemia relatively more insulin may be required. Similar considerations apply to the pregnant diabetic. Insulin does not appear to be called for in pernicious vomiting of pregnancy.—A. T. C.

**Necropsy findings in diabetes.** Wilder (R. M.), South. M. J. (Birmingham), 1926, 19, 241-248.

The author summarizes his results as follows:

An analysis is presented of the pathologic conditions found in a group of 81 fatal cases of diabetes. Diabetes was solely and directly responsible for death in 10 cases, death in the remainder

being due to degenerative complications or to the consequences of operations. Necropsy was performed in 58 cases. Gallstones were found in 16 of the 58 cases at necropsy. Pancreatic stones were found in 3 cases. Sclerosis of the kidneys occurred in 14 instances, and chronic diffuse nephritis in 4. Arteriosclerosis of considerable degree occurred in nearly all cases when the age of the patient exceeded 40 years. Gangrene accounted for 14 of the 81 deaths and was associated with a high degree of coronary sclerosis and myocardial damage in 75% of cases in which the heart was examined at necropsy. A very high incidence of advanced coronary sclerosis was encountered in the series as a whole (17 cases among 58), associated usually with marked fibrosis of the myocardium. In 4 cases exophthalmic goiter and diabetes were combined. In two of them the pancreas revealed little or no anatomic abnormality. Hydropic degeneration was not recognized, but marked fatty changes in the islands occurred in 11 cases. In several cases, representing the most severe and intensive instances of diabetes in the series, the pancreatic lesions were trivial. On the other hand, severe pancreatic lesions were frequently found in cases of relatively mild diabetes, in which death was due to degenerative complications. A parallelism between the degree of parenchymatous changes and the intensity of the clinical symptoms of diabetes does not exist. The explanation of the cause of diabetes must involve considerations such as heredity of predisposition and ability of cells other than those of the pancreas to elaborate insulin.—J. C. D.

**Function of the parathyroids (Experimentelle Untersuchungen über die Funktion der Epithelkörperchen).** Ogawa (S.), Arch. f. exp. Path. u. Pharmakol. (Leipz.), 1925, 109, 83-107.

The author, using rats and rabbits, undertook to demonstrate the influence of parathyroid and of thyroid function upon the healing of fractures and also upon the calcium deposition within bones. The work attempted was extensive but the number of animals used was not sufficient for all the experiments attempted. He finds that parathyroid insufficiency delays callous formation and calcification, and that these processes are accelerated following parathyroid feedings. Thyroid extirpation caused no noteworthy alterations in callous formation. Thyroid feedings, however, inhibited callous formation. Some increase in weight was observed which was due to a greater water content. Thyroidectomy and subsequent thyroid feedings produced an increase in the water content but a decrease in the ash and calcium percentage of the callous as compared with those observed following thyroidectomy alone. Thyroparathyroidectomy caused a decrease in the weight of the callous, a rise in the water content of the callous, and decrease in the ash and calcium content. Parathyroidectomy followed by acute fetal tetany in rats caused inconstant results as regards the constituents of

bone. There was a decrease in the calcium content which seemed to be related to the acuteness and severity of tetany. The feeding of parathyroid substance caused an increase in the calcium content of bone. Thyroidectomy alone caused a slight drop in the water and the ash content of bone. These values were increased following thyroid feedings. The author finds nothing significant of influence of thyroid function upon the healing of fractures. The retardation observed by others following thyroidectomy is due to parathyroid tissue being removed along with the thyroid. He believes there is an antagonism between the thyroid and parathyroids as far as influencing bone healing is concerned.—S. Shapiro.

**Function of the parathyroids. II. As a heat regulating organ.**

Ogawa (S.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925 **109**, 300-317; Abst., Chem. Abst., **20**, 442.

Extirpation of both the thyroid and parathyroid glands results in a disturbance to the heat-regulating mechanism. In rats and in rabbits the removal of the parathyroids alone interferes with heat control. The injection of parathyroid preparations somewhat compensates for the loss in regulatory function in animals deprived of both thyroid and parathyroid glands, while the injection of thyroid preparation fails to prevent the disturbance. In animals deprived of the parathyroids, as in those lacking both the thyroids and parathyroids, warming is followed by the onset of intense convulsive attacks, but in rats lacking thyroid substance these attacks do not occur if parathyroid tissue remains intact. Thus, the hormone of the parathyroid, but not that of the thyroid, is involved in heat regulation.

**The prevention and cure of tetany by oral administration of magnesium lactate.** Wenner (W. F.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 432-434.

The work was done on parathyroidectomized dogs. Magnesium lactate was given by stomach tube. The magnesium in most cases protects the animal but acts by sparing the calcium and has little direct action in preventing tetany. If the serum calcium falls below 7 mg. per 100 cc. and tetany develops, the calcium defect must be repaired by giving milk or calcium lactate. Magnesium lactate has no effect on the animal until this is done. After a period of forty days' treatment with magnesium lactate most of the animals cease to be in danger of tetany and can eat large amounts of meat without ill effects.—J. C. D.

**The internal secretion of the pineal gland of the rat. (Zur Frage der inneren Sekretion der Zirbeldrüse bei der Ratte).** Hofmann (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **209**, 685-692.

Using Kolmer's method the pineal was completely cauterized

in 5 of 27 young rats, without other marked destructive changes. There followed no noticeable effect on body weight, growth or body fat, and there were no definite appearances of earlier sexual maturity, though the seminal vesicles were enlarged. Heat regulation was not disturbed. Thymus, spleen, testes, pancreas, liver, and kidneys showed no change in relative size.—A. T. C.

**Infantile thymic hyperplasia.** Macneill (N. M.), Arch. Ped. (N. Y.), 1925, 42, 821-824.

Five cases are reported. All of the children were brought to the clinic because of some respiratory difficulty. Following roentgenological treatment there was a marked abatement of the respiratory difficulty. They all showed some thymic hyperplasia before treatment was instituted.—M. B. G.

**The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects.** Boothby (W. M.), Sandiford (I.), Sandiford (K.) & Slosse (J.), Ergebni. d. Physiol. (Wiesb.), 1925, 24, 728-756; Abst., Chem. Abst., 20, 447.

Following the administration of thyroid or thyroxin to two myxedematous and one normal subject there is a temporary rise in N excretion which indicates an increased catabolism of stored protein but which is without effect on true endogenous protein metabolism. With the subject originally in N equilibrium and kept on a constant protein intake, there is an immediate large increase in N elimination with a correspondingly large negative N balance during the period when the heat production is being elevated on account of the administration of thyroxin; however, after the heat production has reached its maximum and is maintained there by small doses of thyroxin, there is a gradual decrease in N output for two to four weeks, until it has reached its former value. Creatinine and uric acid elimination are unchanged following thyroxin although there is a slight excretion of creatine during the period of ingestion when compared with the N loss indicates the breakdown of an albuminous fluid of about 2% N, which is probably responsible for the edema of myxedema. There were no changes in the non-protein N or other N partition products in the blood of the normal after thyroxin; in the myxedematous patients an increased blood urea resulted. The decay curves showing the effect of thyroxin on the basal metabolism with their mathematical formulas are given.

**Bacteriology of the thyroid gland in goiter.** Cantero (A.), Surg. Gynec. & Obst. (Chicago), 1926, 42, 61-63.

Streptococcal flora are predominant. This seems of some significance since enlargement of the thyroid and true thyroiditis are

so commonly noted in diseases due to streptococci or associated with local streptococcal infections.—A. T. C.

**Effect of compound solution of iodin and rest in the surgery of exophthalmic goiter.** Clute (H. M.), J. Am. M. Ass. (Chicago), 1926, 86, 105-109.

In over 200 cases of exophthalmic goiter a compound solution of iodin was given in preparation for thyroidectomy. Sixty-nine of those in whom complete data were at hand were carefully studied. Results of the iodin treatment were analyzed from the alterations in basal metabolic rate and clinical observations. Severely toxic patients dangerously ill are given large doses of Lugol's solution without preliminary metabolism determinations. The drug is given by mouth or by rectum. If necessary it may be given well diluted intravenously or subpectorally. Iodine produces marked histological changes in the thyroid gland. The papillary projections with high epithelium are replaced by vesicles lined by low epithelium and filled with colloid. The degree of involution of the gland varies directly with the iodin content. The degree of hyperplasia is inversely proportionate to the iodin content. Marked involution followed iodin feeding in exophthalmic goiter in 87.9% of cases. There are certain cases, however, that show involution histologically who nevertheless are still very toxic clinically. The effect of iodin on the symptoms of exophthalmic goiter is usually marked. The nervous symptoms are especially affected. The tremor and exophthalmos often disappear. The unrest and nervousness become less. The delirium clears up. Gastro-intestinal crises usually disappear. The basal metabolism in this series averaged +77 before iodin and rest in bed. After 8 to 10 days it fell on an average 30 points. Before the use of iodin and rest only 38% of our cases could have a subtotal thyroidectomy in one stage. Since the use of iodin and rest 63.7% have been operated upon in one stage. Iodin and rest in bed have practically eliminated pole ligations from our list of operative procedures. Only 13% in this group of 69 patients were ligated before thyroidectomy. Before the use of iodin and rest 51% had preliminary ligations. Only one pole ligation was performed in our clinic in 1925. Ligation is of little value after iodin and rest in bed in reducing the basal rate. Only 7.2% of these subjects failed to show an appreciable drop in metabolism after the use of iodin and rest. The results following subtotal thyroidectomy in one operation or when divided into two hemithyroidectomies are similar. Iodin administered over long periods without thyroidectomy does not cure exophthalmic goiter. Thyroidectomy must be added to iodin and rest in bed in the treatment of exophthalmic goiter to produce a return to normal health.

— Author's Abst.

Syndromes of hypothyroidism and obsessive syndromes (Sindromi di ipotiroidismo e sindromi obsessive). Coppola (A.), (Siena), 1925, S. Bernardino.

Coppola tries to explain the pathogenesis of these apparently paradoxical syndromes, as found in two subjects undoubtedly affected with hypothyroidism. He begins by discarding the "unstable thyroid" of Levi and Rothschild as a factor, because at autopsy in one of the subjects no thyroid was found. According to the author the syndrome of psychic incoercibility is not necessarily of hyperthyroidal origin. Given a predisposition to such symptomatology, which has been hidden by existing hypothyroidism, thyroid medication will establish the syndrome.—G. Vercellini.

Hyperthyroidism in children. Dinsmore (R. D.), Surg. Gynec. & Obst. (Chicago), 1926, 42, 172-176.

Report of a series of cases, the subjects ranging from 5½ to 14 years. The disease is considered to be commoner among children than is usually supposed. A small percentage of cases of the disorder follows acute infection, but there is usually no tangible factor to which the disease can be attributed. The onset is abrupt and the clinical course rapid. Induced hyperthyroidism may follow the prophylactic use of iodine in a very small percentage of cases, but can usually be controlled by discontinuance of the iodine. Such hyperthyroid children are extremely susceptible to all kinds of operative procedure. Where there are other foci of infection the goiter should be removed first, the other foci of infection subsequently.—A. T. C.

The care of the handicapped goiter patient. Dinsmore (R. D.), Surg., Gynec. & Obst. (Chicago), 1926, 42, 177-179.

Myocardial changes, hyperthyroid children, adenomata of long standing in old people, and intrathoracic goiters are considered. By the employment of absolute rest in bed with sedatives, of large quantities of fluid, of blood transfusions (especially in delirious patients) of Lugol's solution, of guarded doses of digitalis, of local anesthesia, with light gas-oxygen anesthesia or analgesia, of a multiple stage operation performed in the patient's room, the handicapped goiter patient has the advantages of manifold measures for his protection. The maximum improvement after Lugol's solution is apparently on the eighth day. It is considered advisable to delay operation for further four days, since sometimes the patients appear to be in better condition at the eighth day than is actually the case.—A. T. C.

Substernal thyroid. Felberbaum (D.) & Finesilver (B.), Am. J. M. Sc. (Phila.), 1926, 171, 218-227.

From a review of the literature and personal study of cases, of which seven are reported, the authors conclude that substernal thyroid is more frequent than is usually believed. Any shadow in the upper mediastinum, which shows a distinct line of demarcation, and is separate from the aorta, is usually a retrosternal goiter. Fluoroscopic examination reveals the absence of expansile characteristics. The mass moves with the trachea during respiration. A visible goiter, plus signs of compression; or signs of compression, plus thyrotoxic symptoms, are indicative of a substernal goiter. Auricular fibrillation associated with indications of a mass behind the manubrium sterni points toward the existence of a substernal thyroid.—R. G. H.

**A comparative study of the effect of two different preparations of iodine upon the preoperative basal metabolic rate in exophthalmic goiter.** Fitzgerald (R. R.), *Canad. M. Ass. J. (Montreal)*, 1926, **16**, 159-161.

Lugol's solution, containing 20 grains iodine to the ounce, was compared with a solution of iodine in hydriodic acid containing 100 mg. iodine per cc. Both solutions effected lowering of the basal metabolic rate in nearly all cases to the same extent and in the same time, but it was necessary to give nearly four times as much iodine in the hydriodic acid to produce the same clinical result as with Lugol's.—A. T. C.

**Carbohydrate loss from the liver of hyperthyroidized rats. Evaluation of thyroid preparations (Ueber den Kohlenhydratverlust der Leber hyperthyreoidisierter Ratten. Zugleich ein Beitrag zur Frage der Wertbestimmung von Schilddrüsenpräparaten).** Fukui (T.), *Arch. f. d. ges. Physiol. (Berl.)*, 1925, **210**, 410-426.

A method of evaluation of thyroid preparations is based on the glycogen loss from the liver following thyroid feeding. Muscle glycogen is unaffected. A parallelism between iodine content and thyroid activity is not shown by this test, though some preparations with very low iodine content were found inactive. Injection of sodium iodide did not produce the effect. Iodalbacid, given in relatively much greater doses, produced a marked lowering of liver glycogen.—A. T. C.

**Total thyroidectomy in thyrotoxicosis of the exophthalmic type. A preliminary report.** Gilman (P. K.) & Kay (W. E.), *Am. J. M. Sc. (Phila.)*, 1926, **171**, 239-245.

In view of frequently encountered disappointing final results and on the principle that diseased tissue should be removed, the authors performed complete thyroidectomy in ten cases. The evidence so far accrued indicates that in selected cases, at least, a total thyroidectomy is indicated. For all cases requiring operation

a much larger amount of thyroid gland should be removed than is at present usually done, as it is believed that the entire gland is diseased and normal should be substituted. The postoperative reaction appears to be inversely proportionate to the amount of gland removed. This apparently applies likewise to the period of convalescence. It is difficult in cases of total thyroidectomy to maintain a proper thyroid balance with a thyroid preparation, if regulated from time to time by basal metabolic determinations. A number of these patients are able to determine subjectively the amount of thyroid extract they require. In seemingly hopeless cases of exophthalmic goiter the results of total thyroidectomy have been most gratifying. The patients after long periods of complete invalidism have resumed their usual occupations and enjoy good health. While total thyroidectomy has been confined for the most part to those patients who were seemingly hopeless and had been invalids for long periods of time, it is felt that the procedure may be extended to embrace less severe cases. The grounds for the belief are that: (1) the entire gland is diseased; (2) the amount to be removed is indeterminate and the subsequent action of the amounts of gland remaining is likewise indeterminate.—R. G. H.

**Method of palpating lobes of thyroid.** Lahey (F. H.), J. Am. M. Ass. (Chicago), 1926, 86, 813-814; Abst., A. M. A.

The method of palpating the thyroid lobes employed by the author consists first in elevating the patient's chin, thus throwing the larynx and trachea forward. Then the chin is rotated slightly toward the side on which the lobe of the thyroid is to be palpated, relaxing thus the sternomastoid on that side and permitting the examining fingers to press deeply in behind it. The original and valuable portion of the method consists in placing the ball of the thumb against the lower lateral portion of the thyroid cartilage and the upper ring or two of the trachea. The trachea is then dislocated laterally, as far as possible without causing choking. By this maneuver the lobe of the thyroid on the side opposite the pressing thumb is moved outward, together with the dislocated larynx and trachea, and is made prominent on that side of the neck. The fingers of the hand opposite that of the one whose thumb is making counterpressure now press deeply inward behind the sternomastoid and behind the thyroid lobe, and the thumb of that hand is brought over the anterior surface of the gland anterior to the sternomastoid. The dislocated lobe may then be palpated between the two. If any difficulty is experienced in distinguishing that the structure grasped between the fingers and the thumb actually is thyroid, the patient may be requested to swallow, when the lobe will be felt to fall and rise between the thumb and fingers of the examining hand, giving information not only as to its thickness and consistency, but also as to its upper and lower limits. The fingers then being oriented as to

the location of the lobe, greater dislocation of the thyroid cartilage and trachea by increased counterpressure may be made and, if necessary, a deeper grasp taken with the fingers and thumb on the dislocated lobe. Lahey says that the advantages of this method of palpating the thyroid lobe are most marked when the thyroid enlargement is slight or doubtful, as particularly occurs in cases of doubtful exophthalmic goiter. It is of value also when one wishes to determine whether or not local enlargements of the thyroid are adenomatous or malignant in character. In making lateral pressure with the thumb, care should be taken to see that the pressing thumb is placed largely against the thyroid cartilage, for if pressure is made largely on the trachea, as one may demonstrate on himself, choking results. In feeling for the back of the dislocated gland, the fingers must be pressed in deeply well behind the sternomastoid and behind the great vessels of the neck.

**The action of thyroxin on the human organism. I. The influence of respiratory metabolism by thyroxin.** Löhr (H.) & Freydanck (W.), Ztschr. f. d. ges. exper. Med. (Berl.), 46, 429-442; Abst. Chem. Absts., 20, 780.

Synthetic thyroxin (Squibb), on intravenous or intramuscular injection, greatly increases oxygen metabolism. The body temperature may or may not be raised, but the increased oxidation bears no relation to changes of body temperature. There is no effect on blood pressure or activity of the heart. In myxedematous patients thyroxin is especially effective and increases oxidation with a rapidity not seen after the use of any thyroid preparation. Small doses can bring oxygen metabolism to normal, with an improvement on the symptoms of myxedema.

**Anemia in hypothyroidism.** Mackenzie (G. M.), J. Am. M. Ass. (Chicago), 1926, 86, 462-464.

Three cases are reported in some detail and 14 summarized as to blood findings. Two of the three patients with hypothyroidism in whom anemia was the most conspicuous clinical fact, had no or very slight characteristics of myxedema, such as increase in weight, puffiness of the face and thickening of the skin, mental impairment, alteration in quality and quantity of hair and constipation. The most conspicuous symptom was weakness; sensitiveness to cold, decreased perspiration, paresthesia of the extremities, palpitation and dyspnea on slight exertion were also noted. The pallor of these patients may be characterized by a distinctly yellow tinge, particularly noticeable about the eyes and malar regions. One patient showed an absence of free hydrochloric acid in the gastric contents. The blood picture suggested primary anemia, but alteration in the size and form of the red cells was slight or entirely lacking in the patients observed, and there was no increase in the urobilin excretion.

tion. The basal metabolic rate before treatment was between —18 and —44. Treatment with thyroid gland was followed in one case by a prompt and complete recovery and in two others by marked improvement. From these three cases and from those reported by Warfield and Greene, it is clear that thyroid deficiency occasionally causes severe anemia resembling either chlorosis or primary anemia, without proclaiming itself by the usual signs and symptoms of myxedema.—R. G. H.

**Hyperthyroid experiments in dogs. I. The physiological evaluation of thyroid preparations (Hyperthyreoidisationsversuche an Hunden. I. Zugleich ein Beitrag zur Frage der physiologischen Auswertung von Schilddrüsenpräparaten).** Mark (R. E.), Arch. f. d. ges. Physiol. (Berl.), 1925, 209, 437-464.

Normal adult dogs were fed a nitrogen-free diet along with various thyroid preparations, and as measures of activity the increase in nitrogen excretion, degree of diuresis, pulse frequency, and loss of weight, were used. Iodothyron, compared on equal iodine content, is more active than fat-free thyroid preparations.—A. T. C.

**Hyperthyroid experiments on dogs. II. Action of thyroid preparations on the growing organism (Hyperthyreoidisationsversuche an Hunden. II. Wirkung von Schilddrüsenpräparaten auf den wachsenden Organismus).** Mark (R. E.), Arch. f. d. ges. Physiol. (Berl.), 1925, 209, 693-704.

Young dogs up to the age of about 16 weeks do not react to large amounts of thyroid preparations given by mouth, whether tested by protein decomposition, pulse frequency, diuresis, or loss of weight. Such a result parallels the fact that children to a certain stage react much less to thyroid than adults. The creatine excretion in young dogs is not influenced by large amounts of thyroid.

—A. T. C.

**Specific dynamic action of nutrient substances. II. Action of carbohydrates and of fats and operation of the active principle of the thyroid (Ueber die spezifisch-dynamische Wirkung der Nahrungsstoffe. II. Die spezifisch-dynamische Wirkung der Kohlhydrate und der Fette. Zuzüglich ein Beitrag zur Frage der Wirkungsweise der Schilddrüsenstoffe).** Miyazaki (K.) & Abelin (J.), Biochem. Ztschr. (Berl.), 1924, 149, 109-135.

Using rats, the authors have determined the influence on the respiratory metabolism of feeding with sucrose, glucose, levulose, and "levoglucosan" for carbohydrates and butter, lard, cocoa butter and olive oil for fats. Simple feeding experiments are contrasted with those in which thyroid administration supplemented the specific food stuff. Both respiratory quotients and energy production were measured. Very complete protocols of the individual experiments

are presented in tabular form. The principal conclusions are: Similar to the results with protein, thyroid feeding increases to a marked degree the specific dynamic action of cane and grape sugar Levulose alone does not affect the respiratory quotient, but thyroid feeding produces a large increase. The author draws a certain parallel with diabetics who show a normal sugar curve with levulose, while normal individuals show little if any hyperglycaemia with levulose test meals. The administration of insulin to a diabetic produces a normal curve, while the joint administration of levulose with thyroid extract gave similar results in the present studies. (Abstracter's Note.—As the shape of any sugar curve is determined solely by the relationship of the dose of sugar to the individual's tolerance, the patent explanation of these phenomena is: In the diabetic with insulin the test meal is a less massive supertolerance dose and hence conforms more nearly to the normal; while with the thyroid feeding the tolerance is lowered; the test meal becomes relatively larger in supertolerance and thus the ordinary flat curve of levulose tends toward the pointed curve of heavy supertolerance dosage.) Levulocasan with or without thyroid does not change the respiratory quotient. Gland administration, however, does increase the specific dynamic action. Animal and vegetable fats alone are without influence on the specific dynamic action. With thyroid feeding they show a 20% increase. On fat-rich diets thyroid feeding produces a less significant increase than with other dietaries. A mixture of phosphate and cane sugar increases the action of the thyroid material. The authors conclude that so-called specific dynamic action depends more on condition and reaction capacity of the organism than upon the food stuff. The differences observed between carbohydrate, fat and protein tend to disappear under the stimulus of thyroid feeding. They deduce that the thyroid influences chiefly the anabolic phase and that the equilibrium existing between syntheses and energy production are disturbed by thyroid excess, the storage phase becoming less and the energy production phase greater.—A. W. R.

**The relationship of endemic goiter to certain potential foci of infection.** Olesen (R.) & Taylor (N. E.), Public Health Reports (Washington), 1926, 41, 557-571.

Examinations were made of the teeth and tonsils of 1,341 white boys and 1,576 white girls in eight schools in Cincinnati for the purpose of determining whether there was a relationship between potential foci of infection and thyroid enlargement. Records were kept of slight and marked thyroid enlargements as well as of slight and marked decay of teeth. In addition, there were recorded the number of apparently normal tonsils, the absence of tonsils through operation, hypertrophy, and cryptic degeneration. Slight thyroid enlargements prevailed to the extent of 37.2% among the boys and

50.4% among the girls. Both moderate and marked enlargements were approximately seven times more prevalent among the girls than among the boys. In the group studied, slight and marked dental decay is no more characteristically associated with thyroid enlargement than with normal thyroid status. Furthermore, the degree of thyroid enlargement appears not to be dependent upon the amount of dental decay. Normal tonsils were found more frequently among both boys and girls with thyroid enlargement than among those with normal thyroids. Approximately one-third of the children examined had had their tonsils removed by operation. A slightly greater percentage of thyroid-normal children had had their tonsils removed than those in whom the thyroid was enlarged at the time of examination. While differences may be noted in the several age groups as regards absence of tonsils, removal often being associated with a higher percentage of thyroid-normal individuals, the evidence is suggestive rather than striking. Enlargement of the tonsils was found more frequently among boys and girls without thyroid enlargement. While some of the evidence concerning hypertrophy of the tonsils in the several age groups is suggestive, the data are too uneven in trend to be convincing. There was no consistent evidence of correlation between cryptic tonsils and thyroid status. Marked thyroid enlargements among the girls are not associated with enlarged or cryptic tonsils as often as are slight thyroid enlargement. The size of the thyroid enlargement is probably independent of tonsillar or dental conditions. Based upon the material gathered during the present investigation, it is believed that there is no definite relation between thyroid status and potential foci of infection presumably located in decayed teeth and enlarged or cryptic tonsils.

The number of children included in the present survey was small and the observations were subject to manifest limitations. Before the relationship between thyroid enlargement and potential foci of infection in the teeth and tonsils can be regarded as definitely determined, it is desirable that additional studies be made in other sections of the country on a more comprehensive scale and possibly with different methods. Nevertheless, it is felt that in so far as the present study is concerned, such a relationship is non-existent.

**The vital capacity in hyperthyroidism.** Rabinowitch (I. M.), Boston M. & S. J., 1926, 194, 199-201.

Twenty-two hundred observations were studied statistically. The vital capacity is reduced in hyperthyroidism. The increase in respiratory rate found in such cases is an effort of the body to maintain a normal oxygen intake and carbon dioxide output in the face of the increased metabolic rate and reduced vital capacity.

—J. C. D.

**Prognosis in exophthalmic goiter.** Read (J. M.), Am. J. M. Sc., (Phila.), 1926, 171, 227-238.

From a personal study of 100 cases Read concludes that acute cases of exophthalmic goiter with well-defined onset offer a more favorable prognosis for recovery than those with insidious onset and symptoms existing for several years before seeking medical advice. The height of the basal metabolic rate offers only slight assistance in estimating the prognosis. Males with exophthalmic goiter seem more resistant to treatment and are more apt to become chronic sufferers than are females. Subtotal thyroidectomy nearly always produces a remission of the diseases if the patient survives the operation, but it does not constitute a cure.—R. G. H.

**Bone formation in the thyroid gland.** Seelig (M. G.), Surg. Gynec. & Obst. (Chicago), 1925, 41, 794-797.

Case history of extensive calcification in the thyroid.  
—A. T. C.

**Aids in predicting the degree of postoperative thyroid reaction: a study based on 1,000 consecutive cases.** Sise (L. F.), Surg. Gynec. & Obst. (Chicago), 1925, 41, 57-62.

In the great majority of toxic thyroid patients under nitrous oxide-oxygen anaesthesia a postoperative reaction is indicated proportional roughly to the increase above normal in pulse rate, pulse pressure, systolic blood pressure, and respiration. With a small proportion of patients in a more advanced condition the reverse holds; this group is asthenic and apathetic, and their operative mortality high.—A. T. C.

**The heart and its management in hyperthyroidism.** Sturgis (C. S.), Rhode Island M. J., 1925, 8, 141-146; Abst. Physical Therapy X-Ray Radium, 7, 187.

In the treatment of patients with exophthalmic goiter and toxic adenomas who have, in addition severe cardiac failure, every resource known to be of value in the treatment of heart disease should be utilized. The patient should be placed in bed and every method used to procure rest. Drug therapy should be used as indicated assisting operative measures. Roentgen ray therapy is worthy of serious consideration in these cases. In a small group of patients according to the author, this therapeutic measure has produced very satisfactory results. The best routine to follow is to give four exposures at intervals of three weeks. The patient is then observed for six weeks following the last treatment. The basal metabolism should be determined at frequent intervals to prevent the possibility of over-treatment and a resultant myxoedema. If striking improvement does not follow four roentgen ray exposures, little

more can be expected of this measure, and further treatment of this nature should be discontinued. This type of treatment is not strongly recommended, as the chances of cure are not great and the period of three months, over which the treatment is given, may be sufficient time in which additional cardiac injury may occur. How often one may hope to relieve cardiac symptoms in these patients is a very difficult question. In the young individual, even though the functional ability of the heart has been markedly impaired, the results are uniformly excellent, provided the underlying pathological condition of the thyroid gland is eliminated. In older patients, even though the cardiac failure is marked, it is possible to produce striking improvement following appropriate therapy directed toward the thyroid gland. These results are so satisfactory that there should be no hesitation in recommending a subtotal thyroidectomy or roentgen ray treatment.

**Morbid anatomy and histology of pellagra.** Susman (W.), Edinb., M. J., 1926, 33, 58-64.

Two cases of pellagra carefully examined at autopsy showed, among other things, changes in the thyroid gland. The author concludes that the oldest lesion is in the thyroid and proliferation of the vesicular epithelium, increased vascularity, and intracellular granularity and a marked fibrosis indicate a disease of the thyroid.

—J. C. D.

**The effect of the administration of thyroxin upon the surface tension of blood.** Wilhelmj (C. M.) & Fleisher (M. S.), Proc. Soc. Exper. Biol. & Med., (N. Y.), 1925, 23, 79-80.

Guinea pigs fed thyroxin showed a fall in the surface tension of their blood. The average change in five days in 27 animals was a fall of 3.7 dynes, the average of the controls a fall of .15 dynes. If thyroxin is added directly to normal plasma there is no change in surface tension. These results agree with previous work in which thyroidectomized guinea pigs showed an increased surface tension in the blood plasma.—J. C. D.

**The status of the heart in myxedema.** Willius (F. A.) & Haines (S. F.), Am. Heart Journal (St. Louis), 1925, 1, 3-7.

One hundred and sixty-two cases of high-grade myxedema were studied with special reference to the cardio-vascular system. It was found that no heart failure and no organic cardiovascular disease cases could be justly attributed to the myxedema. There were numerous electrocardiographic abnormalities which disappeared under thyroid medication. The data presented do not justify the establishment of a cardiac syndrome characteristic of myxedema.

—R. G. H.

Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency. Youmans (J. B.) & Warfield (L. M.), Arch. Int. Med. (Chicago), 1926, 37, 1-17.

Tests of liver function have been made in forty-four patients with thyrotoxicosis. The functional efficiency of the liver was determined by means of the phenoltetrachlorphthalein test as modified by Rosenthal and in a few instances by the levulose tolerance test, the hemoclastic crisis test of Widal, Abrami and Iancovesco, and by the determination of the concentration of the bilirubin in the blood serum. In 28 of the patients tests of the glucose tolerance also were made. Of the patients in this series 22, or 50%, showed an impairment of liver function. Of the 27 cases 21 satisfactorily tested showed a decreased glucose tolerance. No relation was found to exist between the functional efficiency of the liver as tested and the glucose tolerance, basal metabolic rate or other features of the disease except loss of weight. The impairment of liver function in thyrotoxicosis seems to be associated to some degree with loss of weight.—R. G. H.

A thyroid-adrenal interrelationship. Zwemer (R. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 23, 31-32.

Cats deprived of their adrenals in two operations 7 days apart do not live for more than 3 days after the last operation. If the thyroid is removed and the parathyroids transplanted to avoid tetany, the cats live 9 days or more after complete adrenalectomy. If, however, thyroidectomized cats are fed thyroid extract and then subjected to removal of their adrenals, they survive the operation 2 days at most. The author concludes that his experiments demonstrate a functional interrelation between the thyroid and adrenal glands, in that the life of animals deprived of their adrenals can be greatly prolonged or shortened by absence or excess of the thyroid hormone.—J. C. D.

# Endocrinology

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### STUDIES OF THE THYROID APPARATUS. XXXV. THE RÔLE OF THE THYROID APPARATUS IN THE GROWTH OF THE ADRENALS

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#### INTRODUCTION

This paper deals with the growth in weight of the adrenal glands subsequent to thyroid and parathyroid removal from male and female albino rats at the ages of 23, 30, 50, 65, 75 and 100 days. The scope of the investigation and the procedure, methods of analysis and control have been given in previous papers. Suffice it to state that the animals were allowed to grow after the glandular extirpations until 150 days of age, when the various organs were removed and their weights compared with those of their controls. The method of computation leading to an evaluation of the respective rates of growth is given in the thirty-first paper of the series (1).

The mean observed weights of the adrenals of the several groups together with their probable errors are given in Table 1.

From these are computed the percentage increments and the percentage rate of growth of the tests in terms of that of their controls. These values are given in Table 2. It is easier to get an idea of general relations from charts than from tables of figures. I have, therefore, so arranged the percentage rate of growth of the tests in terms of that of their controls in a series of charts, that a visual comparison of the significant features may be had. The flat black columns represent control growth, while the outline columns give that of the tests. The significant contributions found in the literature up to 1923 have been given in two earlier papers (2), (3), and will not be referred to here unless some special need arises. For the reasons given elsewhere the growth response to thyro-parathyroidectomy will be interpreted in terms of thyroid deficiency alone (4).

#### THE EFFECT OF THYROID DEFICIENCY

On Chart 1A and B the growth of the adrenals is compared with that of the body in weight after thyroid removal at the stated ages. It is seen that the initiation of a thyroid deficiency at any time before the pubertal adjustment is in full swing (65 days of age) brings about a retardation in adrenal growth which parallels in direction the change in body weight with change in age at time of thyroid removal. Once the surge in incretory function of the gonads is established and the animal becomes capable of reproduction, the correlation between adrenal response and body weight response is destroyed.

It is, therefore, clear that up to the time when the pubertal development throws into the organism the new factors of influence emanating from the incretory products of the gonads, the growth processes of the adrenals are fundamentally like those of the body as a whole with respect to their reaction to thyroid deficiency. On the basis of the reasoning outlined in previous papers (5), (6), the conclusion is justified that before puberty the growth of the adrenals is not specifically related to thyroid activity.

The factors which come into play at puberty disrupt the simple dependence of the adrenals on the effectiveness of the growth processes of the body as a whole, and turn the organ over to the thyroid. As a result growth is not only stopped, but it is even rendered retrogressive: weight is actually lost

instead of gained. From which the conclusion seems necessary that the growth of the adrenals in the sexually mature albino rat is specifically dependent on thyroid function. Strong support for this conclusion is had from the fact that the adrenal is the only incretory gland which shows a specific positive weight association with the thyroid in the adult rat (7). The coefficient of correlation is  $0.355 \pm 0.059$  in the male and  $0.193 \pm 0.065$  in the female, when the general factors for organ size carried by the body weight and the influences assumed to be exerted by the other glands of internal secretion are held constant by the method of partial correlation.

Now an increase in the degree of growth retardation of the gonads in both sexes occurs when the thyroid is removed in late and post-pubertal stages of development (6). It can be assumed that this means a diminution in incretory function. Moreover the adrenals are positively and specifically correlated in weight with the gonads. The fifth order coefficient is  $0.170 \pm 0.056$  in the male and  $0.453 \pm 0.036$  in the female. This indicates a specific incretory relationship. Riddle (8) has recently demonstrated a similar relation in female pigeons. Hence it is clear that the pubertal and post-pubertal reaction of the adrenals to thyroid deficiency is due to the retardation of gonadal development as well as to the specific adrenal-thyroid incretory relationship. Further support for this idea is had from the fact that the daily percentage rate of growth of the adrenals in the normal rat drops abruptly between the ages of 65 and 75 days to the level characteristic of the adult animal. The change is from 4.0 to 0.2 in the male, and from 5.2 to 1.0 in the female. While this great diminution in growth capacity is of itself a factor in the reaction of the adrenals to thyroid deficiency, the fact that it occurs at puberty justifies the assumption that it is dependent in part at least on gonadal incretory activity, and hence that these are conditioners of the response to thyroid removal.

From Charts 3A and 1A and B it is seen that the growth reaction of the adrenal to thyroid deficiency is both absolutely and relatively with respect to body weight greater in the female than in the male. The fact that this relation is the opposite of that to be expected from the percentage increment in the control rats (Table 2), indicates either specificity of adrenal-

TABLE I  
*The Observed Mean Weights of the Adrenals of the Several Groups of Rats*

THYROPARATHYROIDECTOMIZED						PARATHYROIDECTOMIZED						
Age Series	At Beginning			At End (150 days)			At Beginning			At End (150 days)		
	Ref.	Contl.	Test	Control	Test	Control	Contl.	Test	Control	Test	Contl.	Test
MALES												
23	0.0067 <sup>gm.</sup> ± 0.0003	0.0070	0.0068	0.0256 <sup>gm.</sup> ± 0.0005	0.0235 <sup>gm.</sup> ± 0.0007	0.0068	0.0066	0.0261 <sup>gm.</sup> ± 0.0007	0.0218 <sup>gm.</sup>	0.0006		
30	0.0093 <sup>gm.</sup> ± 0.0003	0.0091	0.0090	0.0263 <sup>gm.</sup> ± 0.0007	0.0206 <sup>gm.</sup> ± 0.0008	0.0092	0.0092	0.0272 <sup>gm.</sup> ± 0.0007	0.0238 <sup>gm.</sup>	0.0005		
50	0.0141 <sup>gm.</sup> ± 0.0002	0.0137	0.0136	0.0250 <sup>gm.</sup> ± 0.0008	0.0185 <sup>gm.</sup> ± 0.0009	0.0138	0.0135	0.0255 <sup>gm.</sup> ± 0.0007	0.0225 <sup>gm.</sup>	0.0004		
65	0.0220 <sup>gm.</sup> ± 0.0010	0.0209	0.0212	0.0261 <sup>gm.</sup> ± 0.0006	0.0200 <sup>gm.</sup> ± 0.0006	0.0213	0.0214	0.0256 <sup>gm.</sup> ± 0.0007	0.0205 <sup>gm.</sup>	0.0007		
75	0.0224 <sup>gm.</sup> ± 0.0004	0.0215	0.0218	0.0254 <sup>gm.</sup> ± 0.0008	0.0216 <sup>gm.</sup> ± 0.0005	0.0219	0.0215	0.0256 <sup>gm.</sup> ± 0.0012	0.0186 <sup>gm.</sup>	0.0007		
100	0.0227 <sup>gm.</sup> ± 0.0006	0.0224	0.0222	0.0243 <sup>gm.</sup> ± 0.0007	0.0192 <sup>gm.</sup> ± 0.0005	0.0224	0.0219	0.0243 <sup>gm.</sup> ± 0.0007	0.0214 <sup>gm.</sup>	0.0005		
FEMALES												
23	0.0073 <sup>gm.</sup> ± 0.0003	0.0071	0.0069	0.0475 <sup>gm.</sup> ± 0.0012	0.0269 <sup>gm.</sup> ± 0.0013	0.0073	0.0072	0.0483 <sup>gm.</sup> ± 0.0021	0.0337 <sup>gm.</sup>	0.0019		
30	0.0083 <sup>gm.</sup> ± 0.0004	0.0082	0.0081	0.0441 <sup>gm.</sup> ± 0.0011	0.0234 <sup>gm.</sup> ± 0.0011	0.0083	0.0082	0.0453 <sup>gm.</sup> ± 0.0012	0.0353 <sup>gm.</sup>	0.0011		
50	0.0147 <sup>gm.</sup> ± 0.0005	0.0141	0.0141	0.0385 <sup>gm.</sup> ± 0.0007	0.0215 <sup>gm.</sup> ± 0.0011	0.0117	0.0114	0.0401 <sup>gm.</sup> ± 0.0009	0.0284 <sup>gm.</sup>	0.0015		
65	0.0264 <sup>gm.</sup> ± 0.0008	0.0257	0.0249	0.0388 <sup>gm.</sup> ± 0.0016	0.0218 <sup>gm.</sup> ± 0.0013	0.0258	0.0253	0.0352 <sup>gm.</sup> ± 0.0013	0.0290 <sup>gm.</sup>	0.0016		
75	0.0294 <sup>gm.</sup> ± 0.0014	0.0285	0.0281	0.0401 <sup>gm.</sup> ± 0.0011	0.0262 <sup>gm.</sup> ± 0.0014	0.0279	0.0280	0.0426 <sup>gm.</sup> ± 0.0019	0.0291 <sup>gm.</sup>	0.0018		
100	0.0368 <sup>gm.</sup> ± 0.0017	0.0356	0.0356	0.0415 <sup>gm.</sup> ± 0.0017	0.0240 <sup>gm.</sup> ± 0.0009	0.0356	0.0351	0.0415 <sup>gm.</sup> ± 0.0017	0.0320 <sup>gm.</sup>	0.0014		

thyroid association or interference from some third factor (7). Since specificity of adrenal-thyroid relationship is not marked until gonad incretory activity is well in force, and since the degree of association between adrenal and ovary is greater than that between adrenal and testis, and since ovary growth is more retarded by thyroid deficiency than is testis growth, the conclusion must be made that the sex differential response of the adrenals is due to an interference on the part of the gonads.

TABLE 2

*The Absolute and the Relative Percentage Rate of Growth of the Adrenals of the Several Groups*

Age Series	MALES			FEMALES		
	Thyroparathyroidectomized Groups					
	Control	Test	T/C	Control	Test	T/C
23	265.7	245.6	92.4	569.0	289.9	50.9
30	189.0	128.9	68.2	437.8	188.9	43.1
50	82.5	36.0	43.7	173.1	52.5	30.3
65	26.3	-5.7	-21.5	51.0	-0.4	-0.8
75	18.1	-0.9	-5.1	40.7	-6.8	-16.6
100	8.5	-13.5	-159.3	16.6	-32.6	-196.6
Parathyroidectomized Groups						
23	288.2	230.3	79.9	561.6	368.1	65.5
30	195.7	159.7	81.1	445.8	330.5	74.1
50	84.8	66.7	78.6	172.8	97.2	56.3
65	20.2	-4.2	-20.9	48.1	14.6	30.4
75	16.9	-13.5	-79.9	52.7	3.0	7.5
100	8.5	-2.3	-26.9	16.6	-8.8	-53.3

\* These figures are positive because control growth being retrogressive gives a percentage decrement instead of increment. The quotient of this into the percentage decrement of the tests is necessarily algebraically positive in sign. The values represent the relative degree of loss of weight, notwithstanding, and are so charted.

The degree of association of the adrenals with the body weight is higher in the adult female than in the male. The values for the coefficient of correlation are  $0.552 \pm 0.043$  and  $0.329 \pm 0.055$ , respectively. This may be a factor in the greater

regression of adrenal weight in the thyroidless females of the 100 day old series (Chart 1A and B).

#### THE EFFECT OF PARATHYROID DEFICIENCY

From Chart 2A it is seen that the initiation of a parathyroid deficiency in the male at any time before the pubertal adjustment is in full swing (65 days of age) brings about a retardation of adrenal growth, which while less in degree, paral-

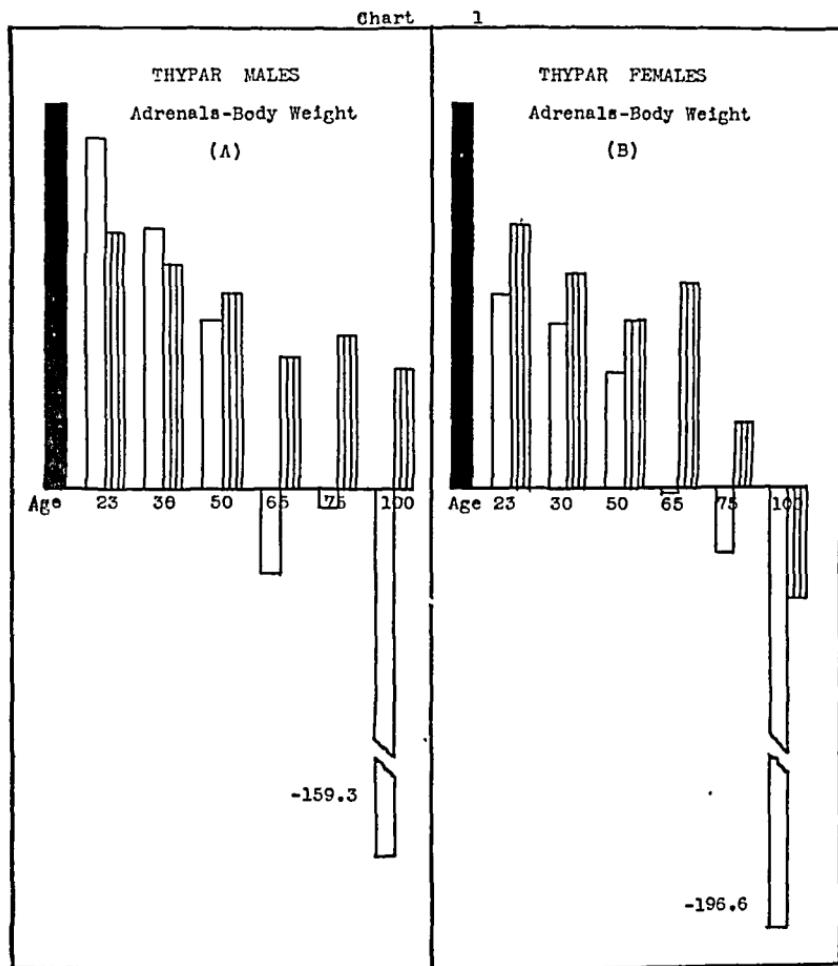


Chart 1. Comparing growth retardation of adrenals and body weight after thyroid removal from A—Males and B—Females at the stated ages. Flat black column represents control growth; outline columns, growth of the test animals. Order of sequence given by the superscript.

lels in direction that of the body weight with respect to the age difference in response. Once puberty is established, however, and the animal becomes capable of reproduction the associa-

tion is ruptured and the adrenal response is in no way comparable with that of the body. In the female, on the other hand (Chart 2B) the growth response of the adrenals, while greater in degree, is quite consistently parallel with that of the body in the direction of change with change in age at time of glandular removal.

The conclusion is that in general the growth processes of the adrenals of the female are similar to those of the body as a whole in their reaction to parathyroid deficiency and are sim-

Chart 2

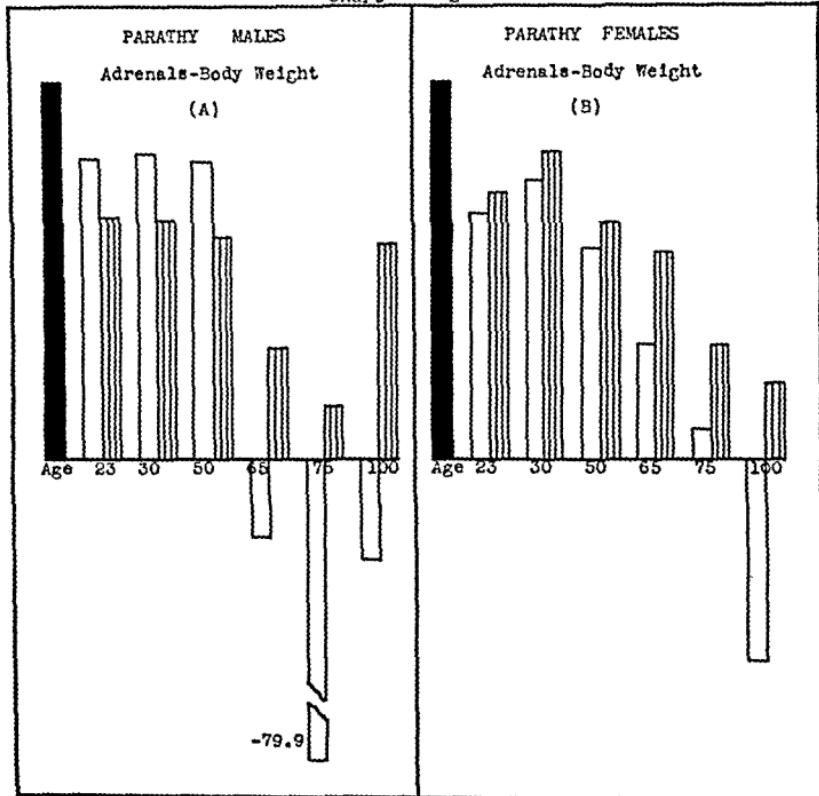


Chart 2. Comparing growth retardation of adrenals and body weight after parathyroid removal from A—Males and B—Females at the stated ages. Flat black column represents control growth; outline columns, growth of the test animals. Order of sequence given by the superscript.

ilarly interpretable, i. e., in terms of a lowered nutritional level (4). The regression of adrenal growth in the 100 day old series is like that which occurs in the case of the ovary (7). From what has gone before it is evident that the extra reaction of the former can be attributed to that of the latter. This raises the question as to whether the general concordance of adrenal re-

sponse with body weight response is due to its dependence on the effectiveness of the growth processes of the body as a whole, or whether it is due to the specific adrenal-ovary association, since the ovary also tends to follow the course of the body weight response. Inasmuch as the adrenal exhibits a closer parallelism than the ovary in this respect, I am inclined to believe that the

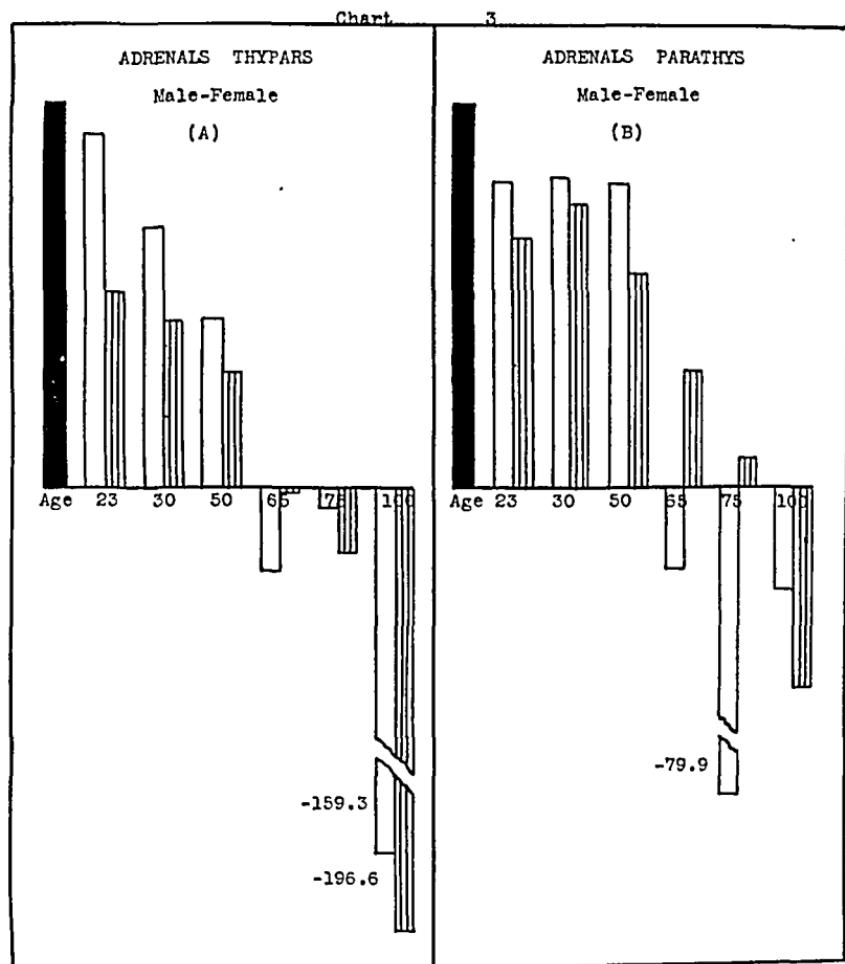


Chart 3. Sex comparison of adrenal response to A—Thyroid removal and B—Parathyroid removal at the stated ages. Flat black column represents control growth; outline columns, growth of the test animals. Order of sequence given by the superscript.

first interpretation is the more valid, at least up to the age of sexual maturity. At any rate it is clear that there is no specific relation between adrenal growth and parathyroid function.

In the case of the males the same conclusion holds true for groups from which the parathyroids are removed prior to the

pubertal surge. The marked reaction which occurs during and after this period shows conclusively that puberty conditions an increased sensitivity to parathyroid deficiency. Since the reaction of the adrenals is so markedly different from that of the body as a whole and of the parts so far studied, it would appear

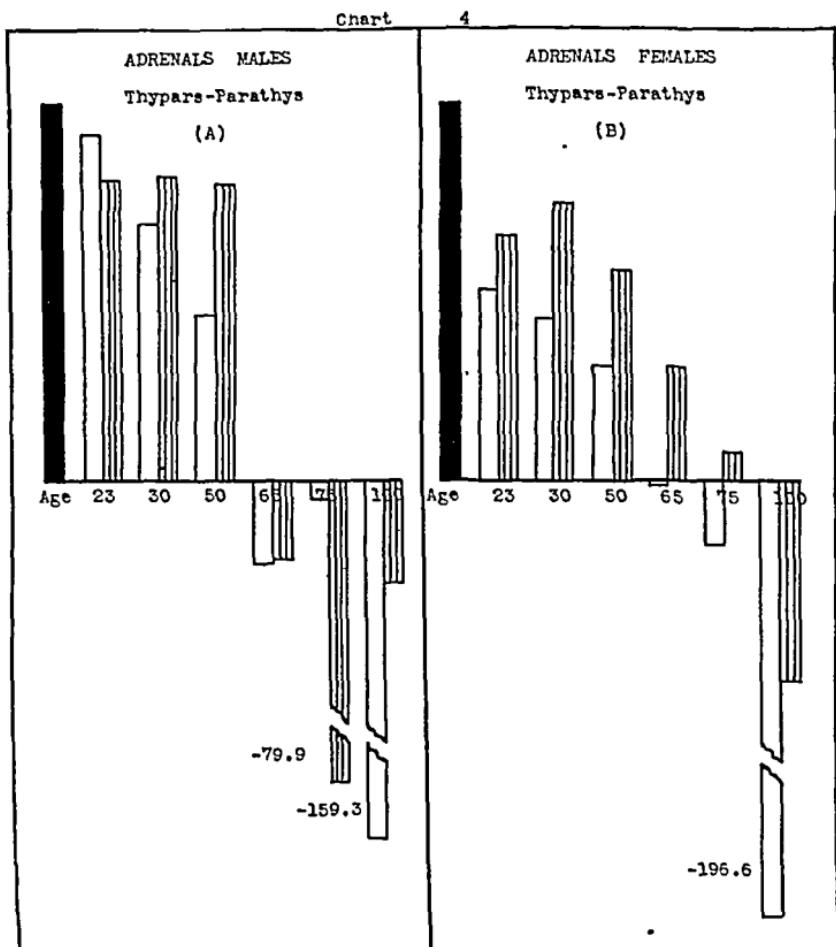


Chart 4. Comparing the effect of thyroid and parathyroid deficiency on adrenal growth in A—Male and B—Female albino rats. Flat black column represents control growth; outline columns, growth of the test animals. Order of sequence given in the superscript.

as if a certain degree of specificity is present. On the other hand, since it is puberty that brings this about, and since the pubertal changes are justly attributable to testicular secretory activities, it would also appear as if it is these changes and their influence on the body and not any specific adrenal-parathyroid secretory relation which is at the basis of the matter.

Perhaps the situation can best be expressed by saying that puberty in the male determines an increased sex-specific sensitivity of the adrenals to parathyroid deficiency. The effect of this is shown on Chart 3B.

From Chart 4B it is seen that the growth of the adrenals in the female is uniformly less disturbed by parathyroid than by thyroid deficiency. In the male the relations are inconstant (Chart 4A). In both sexes, however, the relative influence of the two types of glandular deficiency is the same in direction as that exhibited by the body in weight. Hence it can be concluded that these differences are essentially an expression of the dependency of the adrenals on the relative effectiveness of the growth processes of the body as a whole after thyroid and parathyroid removal.

Now a study of the course of growth in body weight subsequent to thyroid and parathyroid removal (4) led to the conclusion that the growth retardation which ensues is the result of a condition of essential undernutrition in both cases. The question therefore arises as to whether the growth of the adrenals in the thyroidless and parathyroidless rats is like that which occurs in inanition. While a study of the effects of undernutrition on the growth of the adrenals as given by Jackson (9) shows that these organs are markedly influenced by dietary deficiencies, the singular inconstancy of the results indicates that other factors beside that of diet are at work. True it is that an attempt has been made to evaluate the influence of age and sex, but only confusion has resulted since the number of animals used in any given group was too small and the experimental conditions too varied for accurate outcome. These preliminary explorations show that the matter deserves a carefully planned and systematic investigation.

The present state of the subject allows no definite correlation to be made between the adrenal response to dietary undernutrition and that resulting from thyroid or parathyroid deficiency. From Charts 1 and 2 it is clear that in the male the adrenals are less sensitive than the body as a whole to the uncomplicated nutritional deficiency originating from thyroid or parathyroid removal before puberty. Whether a similar sex difference will be found in cases of undernutrition due to dietary deficiency is yet to be determined. That such is possible is in-

dicated from the report of Jackson and Stewart (10) of a sex difference of like direction in rats underfed from three weeks to twenty weeks of age, and then refed for a time.

#### SUMMARY AND CONCLUSIONS

The outstanding facts brought out by this study are that the secretory relationship of the gonads with the adrenals is a major factor in determining the growth response of the adrenals to thyroid deficiency, and that puberty determines a sex-specific sensitivity of the adrenals to parathyroid deficiency in the male.

Other findings are:

1. The growth of the adrenals is not specifically related to thyroid activity before puberty.
2. The growth of the adrenals in the sexually mature albino rat is specifically related to thyroid activity.
3. The growth of the adrenals in the female rat is not specifically related to parathyroid activity.

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STUDIES OF THE THYROID APPARATUS. XXXVI.  
THE RÔLE OF THE THYROID APPARATUS IN  
THE GROWTH OF THE PANCREAS

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INTRODUCTION

This paper deals with the growth of the pancreas of male and female albino rats subsequent to thyroid and parathyroid removal at 23, 30, 50, 65, 75 and 100 days of age. Since preceding papers give the scope, methods and point of view of the investigation as a whole, none of the details need be given here. Attention is called to the fact, however, that the animals were 150 days of age at the time the terminal records were made. Table 1 contains the observed means and probable errors of the weights of the pancreas of the several groups. The computation of the initial "control" and "test" values is described elsewhere (1). Table 2 gives the percentage rate of growth calculated from the data in Table 1. It also gives the percentage rate of growth of the tests in terms of that of their controls (T/C). The comparisons are best made from charts. On these the flat black columns represent control growth (always 100 per cent), while the outline columns stand for test growth in terms of control. The order of sequence is given by the superscript. For the reasons given in another paper (2) the sequelæ of thyro-parathyroidectomy are interpreted in terms of the thyroid deficiency alone.

THE INFLUENCE OF THYROID DEFICIENCY

On Chart 1A and B the growth of the pancreas is compared with that of the body in weight after thyroid removal at the stated ages.

It is evident that the sensitivity of the pancreas is greater than that of the body as a whole; that this relatively greater sensitivity increases markedly at the onset of puberty, weight actually being lost instead of gained; and that the sensitivity of the

TABLE 1  
*The Observed Mean Weight of the Pancreas of the Several Groups.*

Age Series	HYPOPARATHYROIDECTOMIZED						PARATHYROIDECTOMIZED							
	At Beginning			At End (150 days)			At Beginning			At End (150 days)				
	Ref	Contl	Test	Control	Test	Control	Test	Contl	Test	Control	Test	Control		
MALES														
23	0	1290 ± 0 0046	0 1371	0	8337 ± 0 0279	0	5519 ± 0 0231	0	1330	0	1292	0 8466 ± 0 0264	0 6216 ± 0 0175	
30	0	2512 ± 0 0010	0 2458	0	2121	0	7738 ± 0 0230	0	4685 ± 0 0297	0	2195	0 2486	0 8332 ± 0 0267	0 7221 ± 0 0212
50	0	4111 ± 0 0140	0 1006	0	3973	0	8216 ± 0 0281	0	5014 ± 0 0117	0	1028	0 3917	0 8131 ± 0 0231	0 6591 ± 0 0276
65	0	5918 ± 0 0192	0 5631	0	5705	0	8119 ± 0 0161	0	5238 ± 0 0169	0	5729	0 5751	0 8100 ± 0 0142	0 6101 ± 0 0251
75	0	5609 ± 0 0180	0 5692	0	5710	0	8225 ± 0 0246	0	5384 ± 0 0200	0	5784	0 5659	0 8177 ± 0 0198	0 5187 ± 0 0210
100	0	6315 ± 0 0149	0 6229	0	6184	0	7622 ± 0 0205	0	5363 ± 0 0183	0	6229	0 6083	0 7622 ± 0 0205	0 7010 ± 0 0204
FEMALES														
23	0	1379 ± 0 0058	0 1334	0	1308	0	7527 ± 0 0260	0	1232 ± 0 0261	0	1380	0 1364	0 7244 ± 0 0108	0 5614 ± 0 0217
30	0	2602 ± 0 0073	0 2557	0	2532	0	7071 ± 0 0218	0	1000 ± 0 0148	0	2604	0 2557	0 7378 ± 0 0212	0 6693 ± 0 0163
50	0	4168 ± 0 0092	0 4009	0	3998	0	6971 ± 0 0105	0	3909 ± 0 0161	0	1150	0 4095	0 7084 ± 0 0106	0 5800 ± 0 0137
65	0	5667 ± 0 0181	0 5513	0	5352	0	6183 ± 0 0248	0	1525 ± 0 0201	0	5537	0 5429	0 7058 ± 0 0167	0 5338 ± 0 0204
75	0	5676 ± 0 0158	0 5199	0	5124	0	6287 ± 0 0208	0	1308 ± 0 0166	0	5304	0 5104	0 6169 ± 0 0313	0 5457 ± 0 0308
100	0	6185 ± 0 0110	0 6280	0	6280	0	6911 ± 0 0210	0	4923 ± 0 0138	0	6280	0 6185	0 6914 ± 0 0210	0 6152 ± 0 0279

\* "Beginning" values for "control" and "test" groups computed according to method referred to in text.

pancreas like that of the body progressively increases with the increase in age at the time of thyroid removal.

The picture as a whole gives the impression that the growth processes of the pancreas are more dependent upon the effectiveness of the growth processes of the body as a whole, than upon any specific relation to thyroid activity. This is consistent with the fact that the positive weight correlation which exists between pancreas and thyroid ( $0.339 \pm 0.064$  in the male, and  $0.235 \pm 0.070$  in the female) in the adult rat is largely due to body size

TABLE 2

*The Absolute and the Relative Rate of Growth of the Pancreas of the Several Groups.*

Age Series	MALES			FEMALES		
	Thyroparathyroidectomized Groups					
	Control	Test	T/C	Control	Test	T/C
23	508.1	316.3	62.2	464.2	223.6	48.2
30	214.7	93.5	43.6	176.5	58.0	32.8
50	105.9	26.2	24.7	73.9	-2.2	-3.0
65	44.7	-8.2	-18.3	17.6	-15.5	-87.8
75	45.3	-6.2	-13.7	14.3	-20.6	-143.6
100	22.4	-13.3	-59.4	10.1	-21.6	-214.0
Parathyroidectomized Groups						
23	535.8	381.1	71.1	424.9	313.8	73.8
30	234.0	190.5	81.4	183.3	161.8	88.2
50	101.9	67.1	65.8	70.3	41.6	59.2
65	46.6	11.2	24.1	27.5	7.5	27.4
75	41.4	-3.2	-7.8	19.9	1.0	4.9
100	22.4	15.2	68.2	10.1	4.3	42.8

influence, for when this is held constant by the method of partial correlation the association is negligible (0.115 in the male and 0.049 in the female). Moreover, there is no specific weight correlation between the two organs when the assumed influences of the other secretory organs are collectively stabilized for. The 5th order coefficient is 0.063 in the male and -0.010 in the female.

The pubertal and post-pubertal atrophy of the pancreas would seem to indicate a direct conditioning of the pancreas response to thyroid deficiency by the incretory activity of the gonads. Opposed to this is the fact that the weight correlation between gonads and pancreas ( $0.403 \pm 0.051$  in the male and  $0.374 \pm 0.053$  in the female) is largely dependent on body size, for when this is held constant by the method of partial correlation the degree of association drops to 0.083 in the male and 0.129 in the female. On the other hand, the difference in character of pancreas and body weight response in the 65, 75 and 100 day old series shows that a factor other than body size is effective. This can arise from no other organ than the gonads. But there is no significant direct weight association between pancreas and gonads in the sexually mature rat as shown by the coefficients of correlation just given, which are substantiated by the 5th order values (that for the male being 0.093 and that for the female —0.024). These facts lead to the inference that a third factor participates in the reaction. This factor is the adrenals.

It has been shown in an earlier paper (3) that although there is no general specific weight association between the several glands of internal secretion; there is, on the other hand, an indirect association which is mediated by the adrenals. Now the weight correlation between gonads and adrenals is not only somewhat independent of body size, but it is also independent of the influences assumed to be exerted by the other incretory organs. This is shown by the fact that the zero order values of  $0.310 \pm 0.056$  in the male and  $0.647 \pm 0.036$  in the female remain positive both when body weight is alone held constant (0.143 in the male and 0.494 in the female) and when in addition the thyroid, thymus, hypophysis and pancreas are collectively stabilized for by the method of partial correlation. The value for the male is 0.170 and 0.453 for the female. The same is true of the pancreas-adrenal weight association. The zero order coefficients of  $0.367 \pm 0.053$  in the male and  $0.491 \pm 0.047$  in the female are only reduced to 0.225 and 0.293 respectively, when body weight is held constant, and positive specific association is maintained when in addition the gonads, thyroid, hypophysis and thymus are collectively stabilized for. The 5th order value is 0.132 in the male and 0.238 in the female. Positive specific

weight association can be assumed to indicate specific functional association, at least in the quantitative sense.

The values just given show that there is a specific functional as well as weight association between adrenals and gonads, and adrenals and pancreas. The reciprocal relationships of the triad

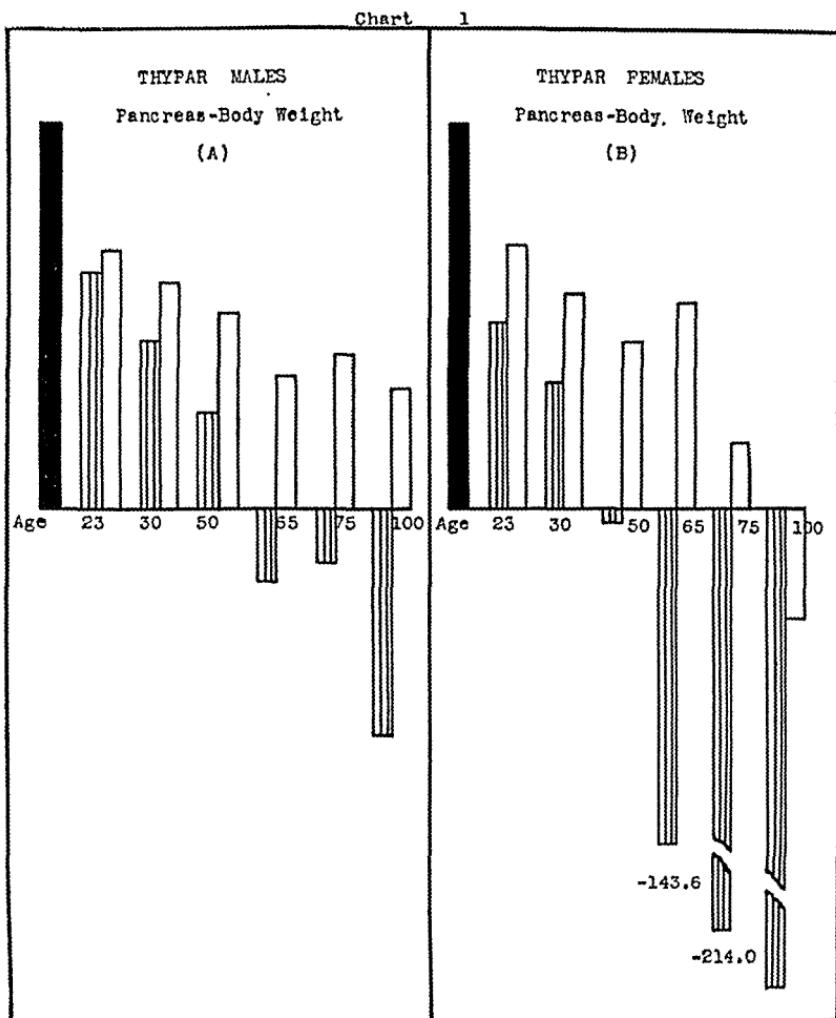


Chart 1. Comparing growth retardation of pancreas and body weight after thyroid removal from A—Males and B—Females at the stated ages. Flat black columns represent control growth (100 per cent); outline columns, growth of test animals in terms of that of controls. Order of sequence given by the superscript.

are represented in the accompanying diagram. This shows that any size relation between gonads and pancreas is conditioned by the adrenals.

Now it was shown in the preceding paper (4) that a pubertal and post-pubertal initiation of thyroid deficiency causes re-

gression of adrenal growth, and that this is largely dependent on the gonads. The evidence would, therefore, indicate that it is this adrenal regression which directly determines the increased sensitivity of the pancreas to thyroid deficiency.

The pancreas should be expected to be more closely dependent on the adrenals than on the gonads from the known fact of the functional interrelations in carbohydrate metabolism, and the fact that thyroid function is also concerned in this phase of organic activity through its participation in the regulation of the metabolic level.

From the foregoing the conclusion is justified that the pancreas shows no specific growth relation to thyroid activity.

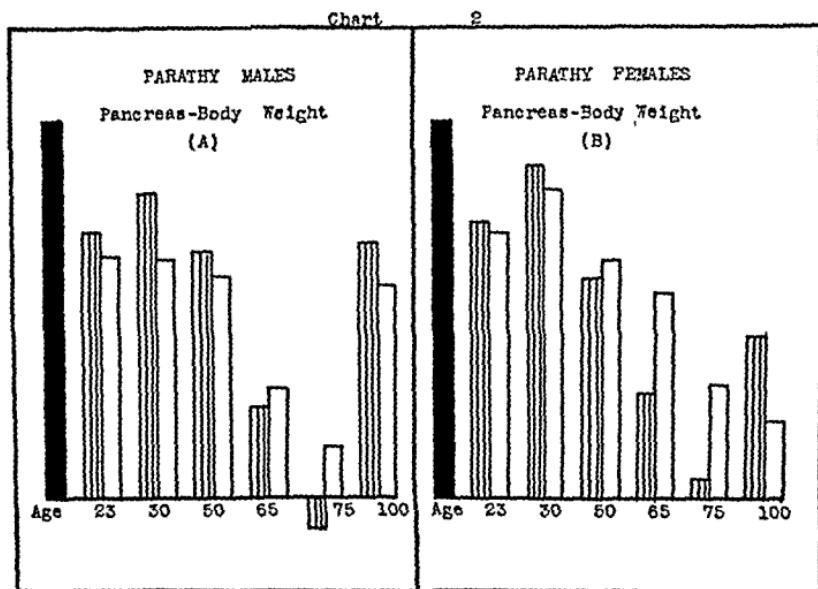


Chart 2. Comparing growth retardation of pancreas and body weight after parathyroid removal from A—Males and B—Females at the stated ages. Flat black columns represent control growth (100 per cent); outline columns, growth of test animals in terms of that of controls. Order of sequence given by the superscript.

A further contribution to the increased sensitivity of the pancreas in the 65, 75 and 100 day old series is the normal cessation of growth of the organ between 65 and 75 days of age (Table 1). The drop in normal growth capacity from the preceding period value of 2.9 in the male and 2.4 in the female is to -0.02 and 0.02 respectively. While the later periods show some slight growth this is very small in comparison to that of the pre-pubertal periods. The rôle of the normal growth capacity in

determining the degree of resistance to thyroid deficiency has been discussed in other papers and need not be repeated.

Now the pancreas is a digestive organ, a large proportion of the metabolic processes of which are concerned in its proper function rather than in the business of growth. It can be as-

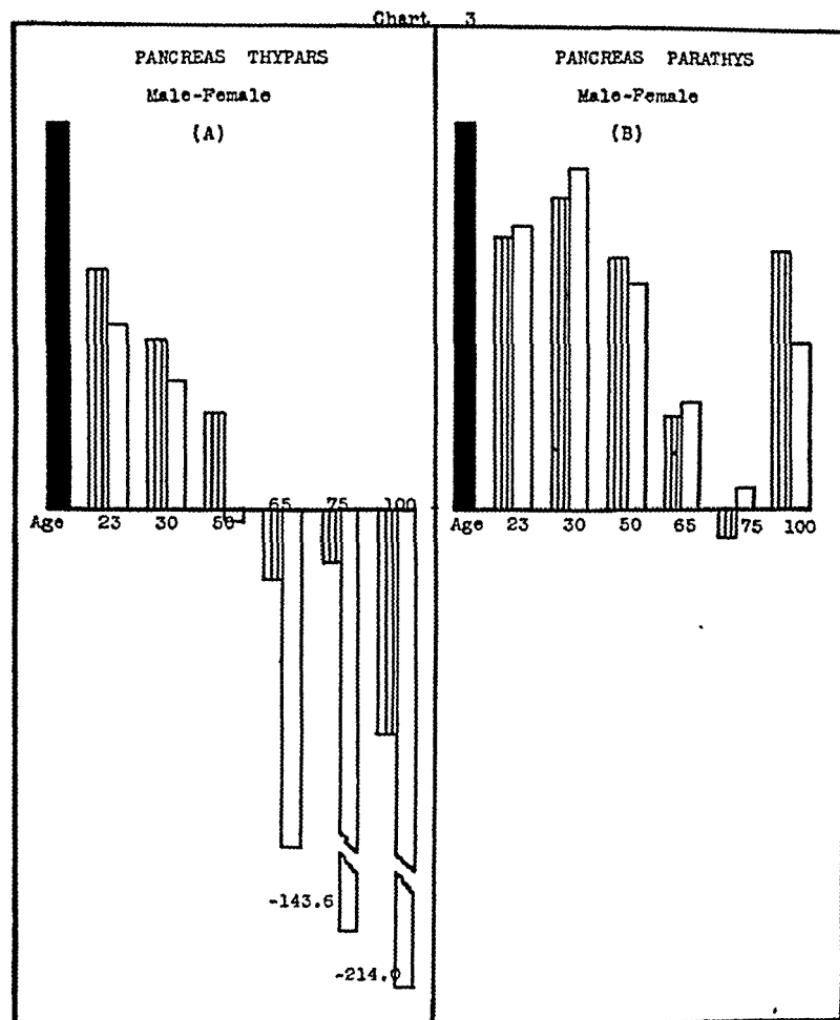


Chart 3. Sex comparison of pancreas response to A—Thyroid removal and B—Parathyroid removal at the stated ages. Flat black columns represent control growth (100 per cent); outline columns, growth of test animals in terms of that of controls. Order of sequence given by the superscript.

sumed that the ratio of the energy used in work done in functional activity and work done in growth is higher in the pancreas than in the body as a whole. This being so, it would be expected, on the basis of the deductions outlined elsewhere (2), that the pancreas would be more sensitive than the body as a

whole to the lowering of the metabolic level consequent on thyroid removal. It would also be expected that the difference would increase, if and when pancreas growth ceases while total function increases and body growth continues. That being consistent with expectation, the foregoing is adequate present interpretation of the pancreas being more sensitive than the body as a whole to thyroid deficiency.

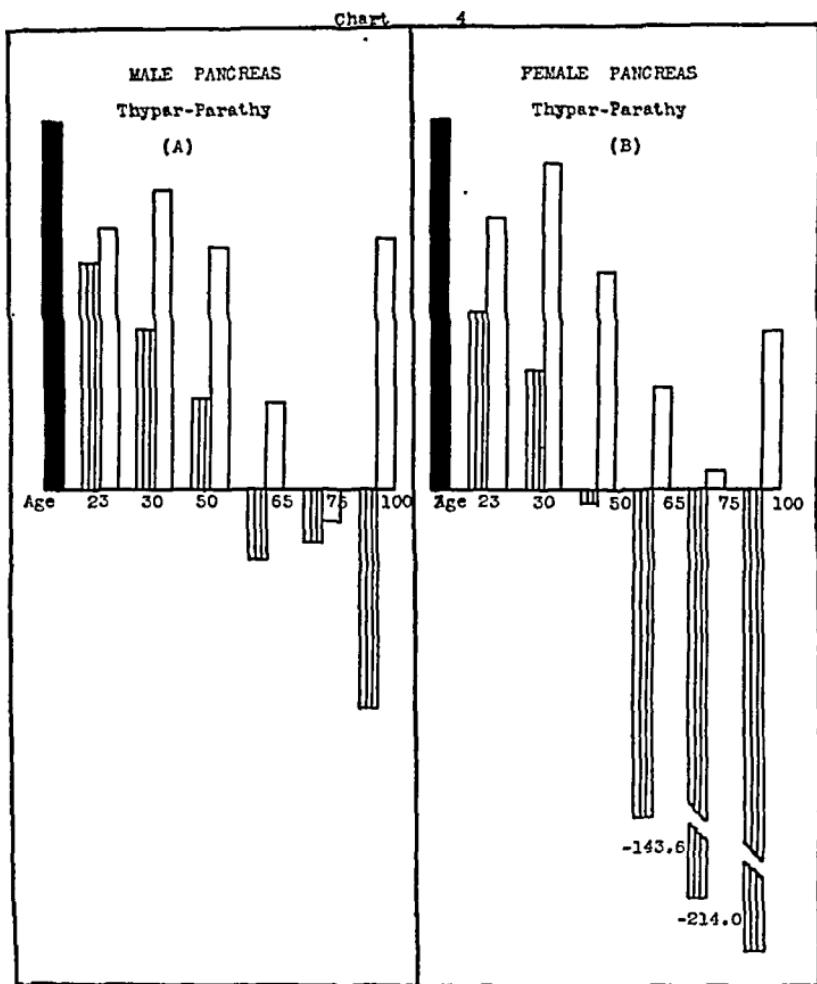


Chart 4. Comparing the effect of thyroid and parathyroid deficiency on pancreas growth in A—Males and B—Females. Flat black columns represent control growth (100 per cent); outline columns, growth of test animals in terms of that of controls. Order of sequence given by the superscript.

From Chart 3A it is seen that the pancreas of the female is more sensitive than that of the male. Since this sex difference increases markedly from puberty onwards it is probable that its

basis lies in large part in the fact that the gonad-adrenal weight association is greater in the female than in the sexually mature male. To this the lesser normal growth capacity of the female pancreas (Table 2) undoubtedly contributes. The discussion of this principle has been given in earlier papers.

Jackson (5) reports that dietary deficiencies in the young produce simple retardation of pancreas growth, while like defects in older animals yield an atrophy. The age differential responses to thyroid deficiency are similar in type. This fact is consistent with the assumption that the growth retardation which follows thyroid removal is fundamentally due to a condition of essential undernutrition (2).

#### THE INFLUENCE OF PARATHYROID DEFICIENCY

An inspection of Chart 2A and B shows that the growth retardation of the pancreas closely approximates that of the body weight in the age differences in response to parathyroid removal. The conclusion is that the growth processes of the pancreas are quite like those of the body as a whole in their relation to parathyroid deficiency and that they are therefore not specifically related to parathyroid activity.

The chart also shows that puberty conditions a change in the relative degree of retardation. It is doubtful if this is attributable to any specific gonad-pancreas relation. Rather it is to be taken as an expression of an individual organic reaction to the general physiological changes produced by adolescence. It is hardly an incretory matter since the direction of difference between pancreas and body weight, once puberty is over, becomes the same (in the 100 day old series) as in the pre-pubertal groups.

Chart 3 B shows that no consistent sex differences are present. A detailed analysis of those which do exist is hardly worth while, since interpretation is impossible.

Turning now to Chart 4A and B where the response of the pancreas to thyroid deficiency is compared with that to parathyroid deficiency, a marked difference in the reaction to the two types of glandular lack is noted.

The pancreas is much more sensitive to thyroid than to parathyroid deficiency. This general difference demands interpretation. I am inclined for the present to believe that its basis lies

in the difference between the two types of metabolic disturbance induced. Thyroid removal primarily determines a lowering of the metabolic level, a secondary effect of which is a lowering of the amounts of material available for growth. Parathyroid removal determines an increased utilization of metabolites and a lowering of the nutritional level (2). The two deficiencies are thus in last analysis provocative of essentially the same condition in so far as growth is concerned: i. e., a state of undernutrition. But the primary metabolic disturbance is in general opposite in character. Hence it is probable that the lesser growth retardation of the pancreas subsequent to parathyroid removal is an expression of a relatively lesser disturbance of the metabolic rate, to which the organ is peculiarly susceptible by virtue of its functional specificity, and also to a lesser diminution in the amounts of material available for growth.

A second matter for clarification is the marked divergence in character of the response to the two types of deficiency when initiated during and after puberty. The reaction to thyroid deficiency, based on direct adrenal interference initiated by gonad response and conditioned by a specific thyroid-adrenal association, is discussed in the preceding section. In the case of the parathyroidless animals the picture is obscure. There is correlation between adrenal and pancreas reaction up to the 100 days old series (4). Here the adrenals undergo atrophy, while the pancreas is only retarded. The adrenals diverge from the body weight response while pancreas growth is less retarded. While the pancreas-adrenal parallelism is only fair in the male, the removal of the parathyroids at 100 days of age produces the same differential reaction as in the female. In view of this fact, and the fact that the pancreas generally parallels the body weight changes with change in age at time of glandular removal, I am inclined to believe that while the adrenals may be a direct factor in the determination of the pancreas response to parathyroid removal, they are only a minor factor, save possibly during puberty. The major factor is the dependence of the pancreas on the effectiveness of the growth processes of the body as a whole.

On the other hand, as shown in an earlier paragraph, there is a positive specific weight, and hence functional, association between pancreas and adrenals in the adult rat. It should be

expected, therefore, that if this is a large factor in determining pancreas response to thyroid deficiency, it should also be evident as a factor in parathyroid deficiency initiated at 100 days. But such is not the case. It is, therefore, clear that a factor is lacking in the adult parathyroidless which is present in the thyroidless groups. The only factor which present evidence justifies us to believe is absent from the one and present in the other is a specific relation between the adrenals and the gland removed. There is a specific association between adrenals and thyroid. There is no proof of a specific relation between adrenals and parathyroid. The tentative conclusion is, therefore, justified that it is the presence of the thyroid-adrenal specific relation-

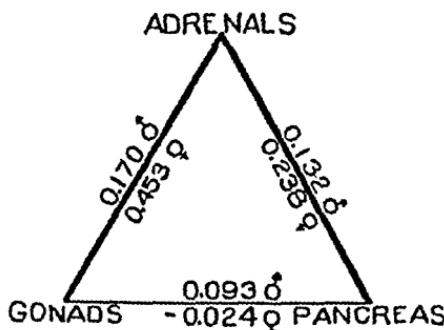


Diagram. Showing the adrenals as the pivotal point of gonad and pancreas relations. The figures are the values for the specific coefficients of correlation unconditioned by body weight, thyroid, hypophysis or thymus.

ship which determines the difference in type of pancreas reaction to thyroid and parathyroid removal at 100 days of age.

Regardless of the uncertainty of the details of relationship in the parathyroidless groups, a few significant facts are clear and these can serve as a starting point for further work leading to ultimate clarification.

#### SUMMARY AND CONCLUSIONS

A study of the pancreas response to thyroid and parathyroid deficiencies indicates clearly that the growth of the organ is not specifically related to the functional activity of either of these endocrine glands.

In the thyroidless groups the dependence on the effectiveness of the growth processes of the body as a whole is the chief pre-pubertal factor determining the growth retardation. During and after puberty, when growth regression instead of simple retardation occurs, the gonads and the adrenal are participants

in determining the increased sensitivity. The connecting specific link is the adrenal.

In the parathyroidless groups the chief factor throughout is the dependence on the effectiveness of the growth processes of the body as a whole.

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# THE OCCURRENCE AND PRESENT CHEMICAL STATUS OF THE FEMALE SEX HORMONE \*

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The chemical identity of the female sex hormone has been established only between certain rather wide limits. The methods of assay are all biological and consist of the following:

1. Noting a growth producing action on the uterus, vagina and breasts of immature virgin rabbits, or of castrated rabbits (Figs. 1 and 2).

2. Noting the change produced by injection of extracts on the vaginal spreads obtained from spayed rats. The vaginal spread of the castrated rat consists mainly of leukocytes. When potent extracts are injected, after an interval of between twelve and forty-eight hours, the spread changes to squamous non-nucleated epithelium similar to the spread obtained from normal rats at estrus (Figs. 3 and 4).

3. Noting the spontaneous, rhythmic contraction rate of the uterus of the white rat when suspended in a chamber filled with Locke's solution. The uterus of the castrated rat has a rhythm identical with that of the early interestrus period of the normal rat. The uterus of a rat whose vaginal smear had become positive by means of injection of potent extracts produces the slower contraction rate typical of estrus in the normal animal (21).

All of these methods are reliable and yield identical results. The method of assay based on vaginal smears, introduced by Allen and Doisy (1), is the most convenient because it does not involve the sacrifice of the animal and the results are available in a much shorter time. The introduction of this method of assay marked a very important advance in the technique for the

\*Read before the Tenth Annual Meeting of the Association for the Study of Internal Secretions, Dallas, Texas, April 20, 1926.

study of the female sex hormone. All of the above methods of assay indicate that the hormone as obtained from the follicle liquid, the corpus luteum, placenta, and blood of animals in estrus is identical. Chemical studies to date lead to the same conclusion.

The occurrence of the female sex hormone in the follicle liquid was first reported by Frank (2). In the follicular liquid the hormone occurs in such quantities that no concentration is necessary, and the pure fluid itself will produce positive results by all methods of assay. Allen and Doisy (8), continuing the work of Frank, have shown that the hormone follows the lipoid fraction of the liquid and have further shown that the hormone can be freed from cholesterol by precipitating the cholesterol with digitonin. Studies on the hormone from the follicular liquid have given us no chemical information which we did not have from studies on the hormone obtained from the corpus luteum and placenta.

The occurrence of the female sex hormone in the corpus luteum has been established by many workers, among them Iscovesco (3), Hermann (4), Frankel and Fonda (5), Fellner (6), Frank and Rosenbloom (7), etc. These workers based their conclusions on the production of hyperplasia and hypertrophy of the uterus of the young immature virgin rabbit and of the castrated rabbit. With the introduction of the vaginal spread method of assay Allen and Doisy (1) report only negative results with their corpus luteum extracts. An obvious explanation is that they were unable to concentrate the active substance found in the crude lipoid extracts. These workers in a preliminary report assumed that the female sex hormone did not occur in the corpus luteum, at least of the hog.

In a second article (8) not only was the presence of the active principle in the corpus luteum denied but doubt was cast on all of the work of other investigators in this field who had reported the presence of the hormone in this body. The following is a quotation from that paper of Allen and Doisy:

"Although all of the authors referred to in the preceding paragraphs who used lipoid solvents may have obtained active extracts from whole ovaries or placenta, their findings of the hyperplastic substance in the corpora lutea casts doubt upon their observations. While it is not in our province to explain this confused situation, we may point out that in some cases it might be attributed to the use of

normal animals in testing for activity. Certainly none of the authors with the possible exception of Hermann has shown that this extract can restore to ovariectomized animals the full growth of the genital tract and the sexual manifestations characteristic of estrus."

This statement was based on the fact that Allen and Doisy were unable to obtain the vaginal spread reaction in spayed rats with their extracts of corpora lutea. Similar findings were more recently reported by Johnston and Gould (9) who failed to get a single positive reaction with 27 preparations of the yellow body. Our studies have shown that larger doses of corpus luteum extract must be given over a longer period of time than if follicle fluid be employed in order to secure hypertrophy of the uterus and mammary glands in either spayed or immature virgin rabbits.

Corpora lutea to the amount of 358 grams were obtained from 1800 grams of freshly slaughtered hogs' ovaries and, after being washed twice with water, were at once ground in a meat chopper and then with sand in an iron mortar. Five hundred fifty cc. of 95% alcohol was added. The mixture was thoroughly shaken and allowed to stand for 48 hours. The mixture was filtered and evaporated under reduced pressure to a watery sludge. This sludge was extracted twice with 50 cc. of benzene. The benzene extract on evaporation gave 2.7 grams of residue. A residue prepared in this manner is called "Stock B." This residue was suspended in olive oil making the concentration 25 mg./cc. An immature virgin rabbit injected with this material on alternate days for two weeks showed hypertrophy of the uterus and mammary glands and the result was indicated as plus 2.

. Stock B was prepared from 545 grams of corpora lutea from 2200 grams of hogs' ovaries taken immediately after slaughter and tested in a similar fashion. The results with some animals, given only four injections, were indefinite. Animals, however, that were given seven injections over a period of two weeks showed a plus 2 reaction.

With the vaginal smear reaction results with the above material were negative with four injections of 25 mg. each and also with four injections of 50 mg. each. This led to intensive study of the preparation of corpus luteum extracts with the result that extracts have been obtained which now give all reac-

tions that extracts of follicle liquid and placenta will give, including the vaginal smear test demanded by Allen and Doisy.

In the preceding experiments the corpora lutea had represented a composite lot; no attempt had been made to classify them. It seemed possible that the hormone content of the corpus luteum might vary with the time that had elapsed since ovulation. Corpora lutea obtained from 4900 grams of ovaries from freshly slaughtered hogs were separated into classes corresponding to early vascularized, later vascularized, flourishing, and involuting; or, more simply, into bloody, bloody pink, pinkish yellow, and yellow.

Samples were taken and analyzed with the following results:

	Bloody	Bloody pink	Pinkish yellow	Yellow
Grams of each class.....	98	484	378	69
Moisture % .....	81	79.9	79.1	75.5
Crude lipoid (% of dry substance) .....	18.6	25.4	36.6	32.2
Nitrogen (% of dry substance) .....	12.6	10.68	10.45	10.38
Phosphorus (as % of pentoxide of dry substance) ..	2.68	3.38	3.44	2.42
Ash (% of dry substance) .	4.63	5.26	4.92	3.95

Stock B was then prepared from each of these classes and suspended in olive oil with a dosage of 50 mg. per cc. Assayed by the vaginal smear test the results were as follows:

Class	Number of injections	Total dosage	Reactions	
			1st animal	2nd animal
Bloody .....	3	150 mg.	negative	negative
Bloody-pink .....	3	150 mg.	negative	negative
Pinkish-yellow .....	3	150 mg.	plus 1	plus 1
Yellow .....	3	150 mg.	plus 3	plus 2

The striking result is the concentration of the active material in the yellow class. Frank has offered the following explanation for these findings (10):

"At the time of follicle rupture a concentrated active extract, the follicle fluid, is poured into the peritoneal cavity and rapidly absorbed by the lymphatics. The granulosa of the follicle at that time has no connection with the blood stream; hence the product is stored. But immediately after ovulation, capillaries penetrate the ruptured follicle, and within a few hours the process of vasculariza-

tion places each secreting cell in intimate contact with one or more capillaries. From that time on the follicle, or better, its successor, the corpus luteum, is no longer a storage gland and the secretion is carried off as soon as formed. When full maturation has been reached or just passed, the blood channels begin to diminish before the secreting cells lose their activity. Therefore, for a short period a sudden transitory increase in the stored active substance is noted."

Concentration of the hormone by means of removal of fats, phospholipins and cholesterol was then attempted with the following results:

Class	Amt. of of crude material injected	Result on spayed rats	Amt. of purified material injected	Result on spayed rats
Bloody .....	150 mg.	neg. 48 hrs.	75 mg.	plus 3, 36 hrs.*
Bloody pink.	150 mg.	plus 2, 48 hrs.	75 mg.	plus 4, 36 hrs.
Pink yellow .	150 mg.	plus 3, 48 hrs.	75 mg.	plus 4, 18 hrs.
Yellow .....	150 mg.	plus 4, 36 hrs.	75 mg.	plus 4, 18 hrs.

More highly concentrated and purified material gave positive results with a total dosage of 45 mg. and 28 mg.

These experiments prove conclusively that the hormone is found in the lipoid fraction of the corpus luteum and that it is more concentrated in the yellow type of corpora lutea. Purified extracts produce hypertrophy of the uterus, vagina and breasts in immature virgin rabbits and in castrated rabbits. They produce the vaginal smear reaction in rats and the uteri of these spayed rats show typical spontaneous contractions in oxygenated Ringer's solution that are characteristic of oestrus. The material was fresh, obtained at the slaughter house and at once worked up. Therefore the possible but improbable objection of post mortem diffusion of follicle fluid into the corpus luteum cannot apply.

In a recent paper Allen and Doisy (11) apparently reverse, in part at least, their position as to the presence of the hormone in the corpus luteum. They state that the corpus luteum in women continues to secrete the hormone for a considerable period of time, even stating that the corpus luteum of the first and third months of pregnancy continues to secrete the hormone. The explanation is offered that the corpus luteum of the primate occupies a different position from that of the rest of the mammals. This is an extraordinary assumption since

\*Pink signifies squamous and nucleated epithelium, no leucocytes present.

the *corpus luteum* is actually found among monotremes in which the uterine portion of gestation is very short.

While our work proves conclusively by chemical methods that the hormone is found in the *corpus luteum* of the hog, this conclusion has been corroborated from a biological standpoint by Zondek and Ascheim (12). These workers implanted small portions of the tissue to be tested in the thigh of spayed mice and studied the effect on the vaginal spreads. Using human material they found no hormone in germinal epithelium, stroma

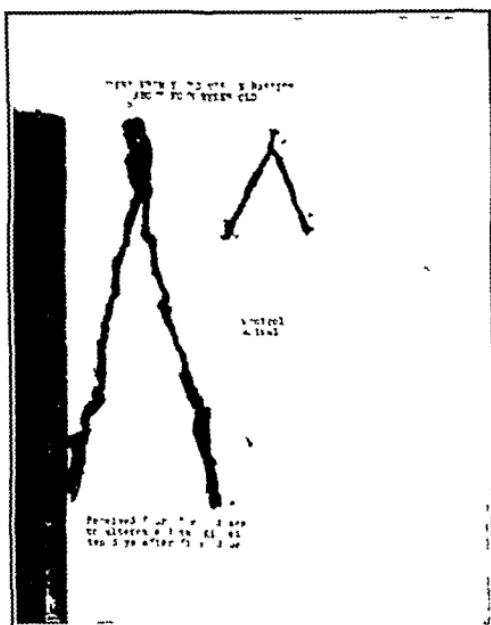


Fig. 1. Uteri from young virgin rabbits about four weeks old.

or primordial follicles. All larger follicles contained the female sex hormone. Implantation of the wall of ripening follicles also gave a positive result. Implantation of the flourishing *corpus luteum* always gave a positive reaction. Tests with liver and other tissues gave negative results.

These concordant results obtained by many investigators by different methods should end this long drawn-out controversy. Positive results based on material obtained with all precautions, assayed by all methods known, and repeated without failures after proper extraction, technic, and dosage had been worked out, must surely outweigh negative reports. The fail-

ures are ascribable to lack of concentration and subthreshold dosage.

As our researches and those of other workers indicate that the hormone found in the follicles, corpora lutea, and placenta are identical, we have used placentae as the base of our further work, because placentae are easily obtainable and contain the hormone in large quantity and are readily extracted. The chemical study of this, as of other hormones, is still far from complete. The question of chemistry resolves itself into two problems:

1. Is the physiologic activity of crude extracts due to the specific substances alone, or can these responses be brought about by other substances?



Fig. 2 (a) Uterus of castile rabbit injected with hormone from placentae (b) Uterus of castile rabbit not injected

2. What is the chemical nature of these specific substances?

Zondek and Robinson (13) have reported the growth of the uterus and vagina of guinea pigs, in response to injections of aolan, histamin, tenosin and epinephrin. Our work, in which immature virgin rabbits were used, gave negative results with these substances. Negative smears were also obtained when we used spayed rats. Schroeder and Goerbig report positive results with liver lipoids (14). We obtain consistently negative

results with liver lipoid. Similar negative results were obtained by Zondek and Ascheim (12) with their implantation technic. The spontaneously ovulating guinea pig is an unsuitable test animal. It was mainly employed by the authors who reported positive results with non-specific substances. In addition the following control materials gave uniformly negative results:

Material	Test used*	Animal	Amt. injected
Olive oil .....	h. u.	rabbit	4 cc.
Ole-one .....	h. u.	rabbit	200 mg.
Ole-one .....	h. u.	rabbit	200 mg.
Liver .....	h. u.	rabbit	200 mg.
Butter .....	h. u.	rabbit	200 mg.
Histamine .....	h. u.	rabbit	6 mg.
Tenosin .....	h. u.	rabbit	
Aolan .....	h. u.	rabbit	
Adrenaline .....	h. u.	rabbit	
Histamine .....	v. s.†	rat	
Tenosin .....	v. s.	rat	
Aolan .....	v. s.	rat	
Adrenaline .....	v. s.	rat	
Brain .....	h. u.	rat	100 mg.
Brain .....	v. s.	rat	100 mg.
Liver .....	v. s.	rat	75 mg.
Liver .....	v. s.	rat	82 mg.
Testes .....	h. u.	rabbit	100 mg.
Testes .....	v. s.	rat	100 mg.
Adrenal cortex .....	h. u.	rabbit	150 mg.
Adrenal cortex .....	v. s.	rat	150 mg.
Adrenal medulla .....	v. s.	rat	75 mg.
Thymus .....	v. s.	rat	100 mg.
Linseed oil .....	v. s.	rat	100 mg.

Assuming the physiologic response to be due to a specific substance, what are its physical and chemical properties? Iscovesco, the pioneer, showed that the lipoid fraction of the placenta contained the active principle (3). Similar results were obtained with the lipoids of the corpus luteum, placenta and follicle liquid by many other workers. Our work has confirmed the statement that the active principle is soluble in lipoid sol-

\*h. u. indicates hypertrophy and hyperplasia of the uterus in young immature virgin rabbits.

†v. s. vaginal smear test on spayed rat.

vents. We also find it to be soluble in water under certain conditions, depending on the presence of other extractives and on methods of purification. Lowe and Laquer report a water soluble preparation of which 1 mg. gave a positive reaction in the spayed mouse (between 1/20 and 1/8 of the rat dose).

In 1915, Hermann reported the isolation of an active preparation from deblooded placenta free from nitrogen and phos-

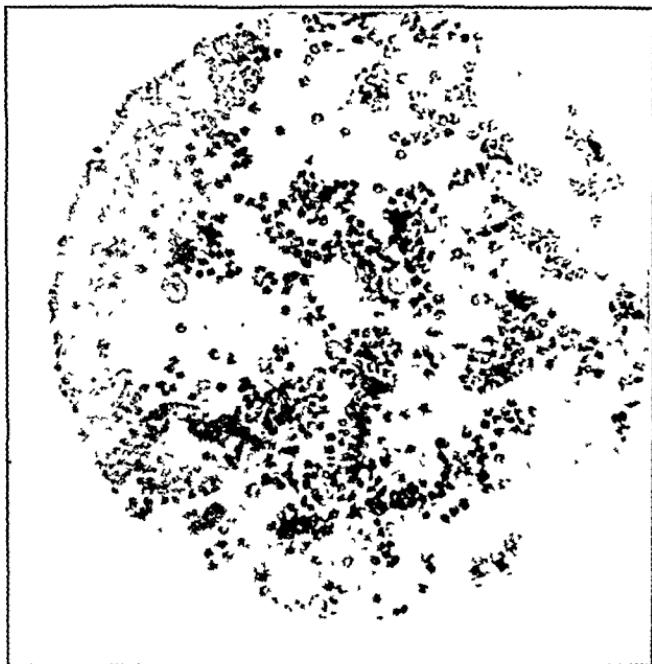


Fig. 3. Cell types found in smear made from castrate rat. Leucocytes.

phorus (4). Frankel and Fonda confirmed this work (5). The most active extracts of Giesy (15) were free from nitrogen and phosphorus. Our work is in harmony with these findings. The preparations of Allen and Doisy contain about 1% nitrogen.

The active substance shows a very high degree of thermostability. All workers are agreed on this property. Herrmann (4), Frankel and Fonda (5), and Frank and Lee have attempted purification by distillation under high vacuum at temperatures ranging from 190° C. to 250° C. without loss of activity. A purified fraction distilling below 100° C. at 30 mm. recently gave us positive results.

The active principle can be extracted from alkaline solutions with ether. This would seem to eliminate acid groups.

It can also be extracted from acid solutions with ether which would seem to eliminate basic groups. Esters seem to be eliminated on the following grounds. Giesy found that the activity was not destroyed by digestion with soy bean lipase. In our work we have saponified the active lipoid fraction with half normal potassium hydroxide, sodium methylate, sodium butylate and sodium ethylate for periods of 72 hours without loss of activity. When the saponified mixtures are evaporated to dryness and extracted with ether, we find that these extracts are physiologically active. In other words, it is either a non-saponifiable material, or, if it is an ester, the activity resides in the alcohol of high molecular weight liberated by the saponification process.

TABLE V

Grams of Stock B.....	.4892	.4874	.4952	.6750	.6656
Cc. 0.5N KOH used.....	50	50	50	50	50
Time of saponification (hrs.)	24	36	48	60	72
Weight of ether extract of					
dried residue .....	.2780	.2660	.1938	.2780	.2390
Results of assay — vaginal					
smear test .....	plus 4				
Mg. injected .....	37.5	37.5	37.5	37.5	37.5
Weight of ether extract from					
dried residue upon acid-					
fying after alkaline extrac-					
tion .....	.1358	.1844	.2390	.3280	.4050
Assay of ether extract of					
acid material .....	neg.	neg.	neg.	neg.	neg.

The results show that the active principle can withstand saponification with alkali for a long period of time without loss of activity. These results are in disagreement with those of Dickens, Dodd and Wright (16), who state that the hormone is slowly destroyed by saponification for 40 minutes in the presence of hydrogen.

Frankel and Fonda (5) report the isolation of the active principle which they describe as thick, viscous light yellow oil with turpentine-like odor, insoluble in water but soluble in all lipoid solvents. They ascribe the formula  $C_{32}H_{52}O_2$ . One atom of oxygen, according to their work, is present in a hydroxyl

group and the other in a carbonyl group. The compound is unsaturated and contains two double bonds. Several derivatives, esters, phenylhydrazone, oxime and tetrabromid were obtained by these authors to substantiate their suggested formula. The pure substance shows cholesterol reactions which Frankel and Fonda take to indicate a relationship to cholesterol and bile acids.

Frank (17) and Doisy, Ralls, Allen and Johnston (18) found that the active principle can be freed from cholesterol and thus a product is obtained which does not give cholesterol reactions. This work indicates that the substance isolated by Frankel and Fonda was at least contaminated with cholesterol. The derivatives of the "pure substance" obtained by them were not



Fig. 4 Cell types found in smear made from castrate rat injected with active hormone preparation from placentae. Squamous epithelial cells.

reconverted into the original compound to see whether the reisolated substance was active. This crucial test would determine whether the derivatives were from impurities or from the pure substance. Work in our laboratories does not substantiate the statement of Frankel and Fonda that the active principle forms a hydrazone.

We have obtained a phenylhydrazone from the lipoid fraction of placenta. The mother liquor after removal of the phenyl-

hydrazone and excess phenylhydrazine is still active physiologically. This might be due to incomplete precipitation. When the phenylhydrazone is decomposed by being allowed to react with glucose, a lipoid is liberated which is inactive physiologically.

The active principle is an unsaturated body absorbing bromine from carbon tetrachloride solution. It is oxidized by exposure to air to a resinous mass darker than the original substance. This oxidation is accelerated by light. The oxidized product is inactive physiologically. This indicates that the active principle is an unsaturated body and not merely associated with unsaturated bodies.

A number of experiments were carried out to test the effect of  $\text{PCl}_1$ , and  $\text{PCl}_3$ , on the hormone. The results are shown in table VI.

TABLE VI

Amount of stock B	Reagent	Amount of reagent	Tempera-ture °C.	Time of heating	Amount injected	Smear reaction
1.056	$\text{PCl}_5$	1.1 g.	145	2 hrs.	100 mg.	neg.
1.15	$\text{PCl}_5$	1.2 g.	110	2 hrs.	75 mg.	neg.
1.10	$\text{PCl}_5$	1.1 g.	110	1 hr.	75 mg.	neg.
1.07	$\text{PCl}_3$	1.2 g.	75	1 hr.	37.5 mg.	plus 4
1.00	$\text{PCl}_3$	1.1 g.	70	2 hrs.	37.5 mg.	plus 4
1.14	$\text{PCl}_3$	1.2 g.	70	2 hrs.	37.5 mg.	plus 4

The destruction by  $\text{PCl}_5$  is apparently by oxidation. The conclusion is confirmed by the fact that after  $\text{PCl}_5$  treatment the lipoid shows a large decrease in the Iodine number, i. e., from 150 to 74. The fact that the active substance is not destroyed by  $\text{PCl}_1$ , would indicate that either the hormone does not contain the hydroxyl group or replacement of the OH by Cl has no effect on activity. Halogens are found in our lipoid preparations only after  $\text{PCl}_3$  or  $\text{PCl}_5$  treatment.

Today we are also able to show that the female sex hormone is present at times in demonstrable quantity in the circulating blood (19). Blood has been collected from hogs in estrus and anestrus. Following the methods developed in connection with the work on placenta and corpus luteum, lipoids have been obtained which, on injection into spayed rats, give the usual vaginal smear reaction. This phase of the problem is still under investigation. Loewe (20) reports similar results.

From the studies up to this time we can say that the hormone may be found in the follicular liquid, corpus luteum, pla-

centa, and blood of females in estrus. The term follicular hormone or ovarian hormone is therefore not sufficiently broad. "Female sex hormone" covers the source of origin as well as the biological function of the substance in question and should therefore be employed. As the hormone can be found in the follicle, corpus luteum and placenta, and as the corpus luteum succeeds the follicle, and the placenta the corpus luteum, the term "gestational gland," as a suitable appellation for this triad, has been suggested.

The active substance is a thermostable lipoid of high molecular weight. It is soluble in all lipoid solvents and also in water under certain conditions. It contains only carbon, hydrogen and oxygen, and possibly merely carbon and hydrogen. It is not an ester or a fatty acid. It does not give cholesterol reactions. It does not contain an active carbonyl group. If it contains the hydroxyl group this group is not essential to its activity. It is an unsaturated compound and is inactivated by attacking the double or triple bonds.

The female sex hormone is a specific substance elaborated by the gestational gland, taken up by the lymph and blood stream and selectively utilized only by Mueller's tract and the breasts.

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# SOME CHEMICAL AND PHYSIOLOGICAL PROPERTIES OF THE HORMONE OF THE LIQUOR FOLLICULI.\*

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## INTRODUCTION

Since the title of this paper may give rise to the question of whether or not the active principle of the placenta and corpus luteum differs from that of the liquor folliculi, we may state at the outset that such physiological data as are available and such chemical data as are admissible for deciding the question indicate the probable identity of the hormone from the three sources. Due to the failure as yet of chemical isolation of the hormone from any source and to the fact that it seems better to us to refrain from a name until a logical one based on its chemical constitution can be given, and since all of the observations described in this paper were made upon liquor folliculi from hog ovaries, we prefer to refer to the product with which we are working as the hormone of the liquor folliculi.

Within the past few months a number of papers upon the ovarian hormone obtained from liquor folliculi have appeared. Most of them appear to be of a preliminary character and therefore cannot be discussed very intelligently. Zondek and Brahm (1925) and Laqueur, Hart, deJongh and Wijsenbeek (1926) agree that the hormone may be obtained in the aqueous filtrate from the deproteinized follicle fluid. This filtrate may be concentrated in vacuo, yielding finally a potent aqueous solution of the hormone.

Laqueur et al. in studying the chemical nature of the solids of their extract have concluded that protein, cholesterol, amino

\*This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association. The authors take this opportunity of expressing their appreciation of the Council's assistance.

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nitrogen, phosphorus, and the hydroxyl group are absent. Some of the extracts obtained contained one mouse unit per 0.01 mg. or even less of solids. Inasmuch as the use of different test animals renders comparison of potency difficult, we cannot definitely assert that this is the most active product thus far reported in the literature, but at any rate this statement is probably correct.

Both Laqueur et al. and Dickens, Dodds and Wright have failed to obtain yields (in physiological units) as large as those reported in our earlier paper (Doisy, Ralls, Allen and Johnston, 1924). Two of us (J. O. R. and E. A. D.), working independently, have made many preparations in which from 500 to 1400 rat units per liter of liquor folliculi were obtained. We suspect that both groups of investigators may have tried to improve our published procedure with the object of obtaining a purer product and in so doing lost some of the efficiency of the extraction process and therefore obtained smaller yields.

Upon still another point the conclusions of Dickens and Dodds disagree with ours, in that they report finding very little more hormone in the liquor folliculi than in an equal weight of ovaries. In this case the findings of Laqueur et al. are in accord with ours. Though we have made only a few preparations directly from whole ovaries during the past two years, we have found nothing to cause us to alter our earlier conclusion that the liquor folliculi of mature follicles contains much more of the hormone than other ovarian structures.

#### PREPARATION FROM LIQUOR FOLLICULI\*

Liquor folliculi collected by aspiration from fresh hog ovaries is preserved with two volumes of 95 per cent alcohol until one liter is obtained. The hormone seems to retain its potency unimpaired under these conditions for as long as sixteen months. The average yield from a large number of preparations is about 850 units per liter of liquor folliculi; from two recent batches, one of which had been kept for six and the other sixteen months, we obtained 1390 and 1200 units respectively.

\*See article by Ralls, Jordan and Doisy in the Journal of Biological Chemistry of August, 1926.

The proteins which are coagulated by the preservation in alcohol are filtered off and extracted in a Soxhlet apparatus; meanwhile the filtrate is being distilled to dryness in *vacuo*. After completion of the extraction, the extract is distilled from the same flask that was used for the filtrate. The dry residue is taken up in about 150 cc. water, any free fatty acids neutralized with sodium hydroxide, and the aqueous solution extracted four times with ether in a separatory funnel. Study of the individual extracts showed that about 80 per cent of the hormone was removed by the first ether extraction and that only 2 or 3 per cent remained in the aqueous phase after the fourth extraction. The ether extracts are combined, washed with dilute alkali and water and then distilled. The dry residue is taken up in 100 cc. 70 per cent alcohol and the cholesterol removed by five extractions of the alcoholic solution with 25 cc. of petroleum ether. This extraction is important for several reasons: (1) The hormone is soluble in the alcohol and only the merest traces pass into the petroleum ether. (2) The reverse is true for cholesterol. (3) Other solids which are present as impurities pass almost completely into the petroleum ether. This advantageous purification removes practically all of the cholesterol and about 95 per cent of the solids, leaving virtually all of the hormone in the alcoholic solution. The alcoholic solution is then distilled to dryness in *vacuo* and the residue taken up in ethyl ether. A small amount of residue which is insoluble in ether may be discarded as it contains little or none of the hormone.

Possibly one or two points in the above procedure deserve comment. We are not at all certain that of all of the possible combinations of solvents those chosen are the most satisfactory, but the method outlined gives a much better product with considerably less work than could be attained by our earlier technique. It is possible that some other concentration than 70 per cent alcohol might lead to better results; this point is under investigation and preliminary data indicate that a product at least four times as potent can be obtained by reducing the percentage of alcohol. One milligram of the preparation thus obtained equals 100-150 rat units, whereas 1 mg. of the solids obtained by using 70 per cent alcohol contains only 25-35 units.

CHEMICAL REACTIONS OF THE HORMONE OF THE 0.04 MG. PER RAT  
UNIT PRODUCT

The heading of this section requires some explanation. We prefer to state conservatively the effect apparently produced by certain procedures upon a product of the potency of 0.04 mg. per rat unit. From certain of our observations, it seems probable that fully 75 per cent and possibly much more of this preparation is not hormone. It is conceivable and indeed probable that certain reactions given by this product may not be given by the pure hormone, hence our caution in the interpretation of results.

## Hydrolysis:

(a) Sodium ethylate. No effect upon potency.

(b) Lipases.

Pancreatic. No effect upon potency.

Liver. No effect upon potency.

Castor Bean. No effect upon potency.

Hydrogenation. No effect upon potency, visible decolorization.

Bromine. Complete loss of potency.

KMnO<sub>4</sub>. Complete loss of potency.

Acetyl chloride. Marked loss of potency.

Benzoyl chloride. Moderate loss of potency.

Naphthylisocyanate. Moderate loss of potency.

Phenylhydrazine. No loss of potency.

Dry heat at 179° at 0.1 mm. for 2½ hours. Over 60% loss of potency.\*

No attempt was made to isolate any of the products which may have been formed, but the reaction was carried out with minimal technical loss, the excess reagent removed and the residue injected into spayed rats.

*Ultimate Analysis:* In the chemical work our available supply of the hormone was so limited that we have had recourse to Pregl's (1923) system of microanalysis; when his methods were not suitable, we have modified them or devised new ones to fit the occasion. The results of our analytical work are given below:

\*Attention should be called to the chemical investigations of Herrmann (1915), Fraenkel and Fonda (1923) and Glesy (1920). Most of the above reactions have been used in their studies of the hormone obtained from the placenta and the corpus luteum; our report is added as a characterization of a product of definite purity made by a clearly stated procedure from hog liquor folliculi.

Carbon, 80.8%; Hydrogen, 10.5%; Nitrogen, 0.93%; Phosphorus, 0.0%; Molecular weight, 458.

#### PROPOSED REQUIREMENT OF A PREPARATION FOR CLINICAL USE

Though we feel certain that the hormone under discussion may be of therapeutic importance, our clinical work has not progressed sufficiently to warrant any conclusions. Organotherapy at present in the ovarian field has both its strong proponents and its vigorous opponents. Both Frank (1922) and Novak (1922) have recently stated that they believed the present day commercial preparations lacked efficacy. We can corroborate their statements with respect to the hormone which produces growth and hyperemia of the genitals. Of a large number of preparations of both foreign and domestic manufacture tested, we have not found one which contained 1 rat unit in three ampoules or in several doses to be taken per os. Of the foreign investigators Zondek (1925) has called attention to the necessity of biological assay and has used the smear method proposed by Allen and Doisy (1923) on mice. He has reported that two of the products tested are potent, and Hannes (1925) using those preparations reports favorable results.

Tentatively we suggest the following requirements for an extract for experimental clinical work: (1) that the hormone be dissolved in an innocuous aqueous medium; (2) that it be assayed by the smear method; (3) that it be ampouled to contain 5-10 rat units per 1 cc.; (4) that ample tests of its sterility and keeping qualities be made; (5) that it should have no effect upon the blood pressure of anesthetized dogs. Taking up these points in the above order:

1. Though we have used "mazola" (corn oil) as the solvent for injection during routine testing, we cannot advocate its injection into patients. Mazola and probably other oils injected subcutaneously produce hard lumps which may slowly disappear or may produce granulomata. We are frequently forced to discard rats which have been used for a number of tests as there is scarcely any good space left for injections. Interesting results upon the local picture produced by the subcutaneous introduction of mazola alone and mazola containing the hormone have been reported by Burrows and Johnston (1925).

From the foregoing it is easily understandable why we prefer aqueous solutions or emulsions for clinical use. As many investigators have stated that the hormone is not soluble in water, it may be necessary to find some agent which will permit the formation of stable colloidal solutions. We tentatively suggest from some preliminary work that a dilute solution of sodium soaps of unsaturated fatty acids in 0.9 percent NaCl might be a satisfactory vehicle for the suspension of the hormone. No ill effects were observable in rats after the subcutaneous injection of such solutions of the hormone.

2. The vaginal smear method of the testing of ovarian extracts (Allen and Doisy, 1923) has proved to be convenient, economical and accurate. Tests of potency can be made in 48 hours on either castrated female rats or mice. Each animal may be used a number of times extending over a period of two or three months.

The accuracy of standardization of extracts will naturally depend upon the observance of a number of conditions and the use of a sufficient number of animals to minimize the errors of biological reactions. Among the factors which may affect the response of the test animal, the following should be mentioned: age, weight, diet, interval between oophorectomy and first artificial oestrous, and interval between artificial oestrous reactions.

In an earlier paper we defined (Doisy, Ralls, Allen and Johnston, 1924) the rat unit as the minimal amount of hormone injected subcutaneously in three equal portions at four hour intervals, which would produce oestrous in a spayed rat weighing from 140-160 gms. It seems that animals of greater weight will require a larger amount of hormone. Loewe and Laqueur, who have used the mouse instead of the rat, report that the mouse unit is from  $\frac{1}{8}$  to  $\frac{1}{4}$  of the rat unit, which is about the ratio of the weight of these species.

As might be expected, pronounced atrophy of the uterus due to lack of hormonal stimulus renders the animals less sensitive, and therefore the results less accurate. We find the most consistent results are obtained by injecting our animals about every sixth day. In case three or four preparations in succession are negative, we find it is desirable to "prime" the rats by

injecting an aqueous solution of hormone which will certainly give an oestrous smear.

Though the enumeration and execution of these various considerations may seem burdensome, the results seem to justify the precautions taken. Loewe has reported that the mouse smear method has an accuracy of 20 percent, and our impression gained from our work is that this figure is approximately correct.

*Table I*

Effect of Sterilization with 15 lbs. Steam for 15 minutes on  
Aqueous Solutions of the Hormone.

No.	Before Autoclaving		After Autoclaving	
	Vol. Injected	Test	Vol. Injected	Test
6b11	0.90 cc. 1.20 :	— +	1.05 cc. 1.20 :	+
G20492	0.07 : 0.10 :	— +	0.10 : 0.15 :	— +
31379	0.15 : 0.20 :	+	0.10 : 0.12 :	±

SYMBOLS: + more than 1 rat unit in volume injected.  
± not quite a rat unit in volume injected.  
— less than 1 rat unit in volume injected.

3. The activity of the preparation to be used clinically is a matter for experiment. Based upon the ratio of the weight of a test rat and a 50 kilogram woman approximately 400 rat units would be necessary to produce oestrous in the latter, if that were possible. We suggest that for experimental clinical work a solution containing 10 rat units per 1 cc. be used. Since it seems from our work with animals that excessive dosage produces no ill effects, any danger to the patient seems very remote. As many as 20 rat units have been injected into a rat without detectable harmful results.

4. Ample tests of the bacteriological sterility are of such well-known necessity that their importance may be dismissed without further comment. The method of sterilization employed may depend upon the stability of the hormone. Mazola solutions may be autoclaved at 15 lbs. for 15 minutes without appreciable loss of potency. Our preliminary data of Table I upon aqueous solutions so sterilized indicate that possibly a slight loss of potency occurs. Autoclaving seems so much easier and safer that we prefer to use this procedure, providing subsequent work

shows that our preliminary observations are correct. In the event that future work shows that the hormone cannot withstand the sterilization with steam under pressure, the Berkefeld filtrate may be used.

During the experimental stages at least, repeated tests should be made to assure oneself of the potency of the solution being used. For our own experimental clinical work we propose to secure a large stock of ampoules filled from the same batch

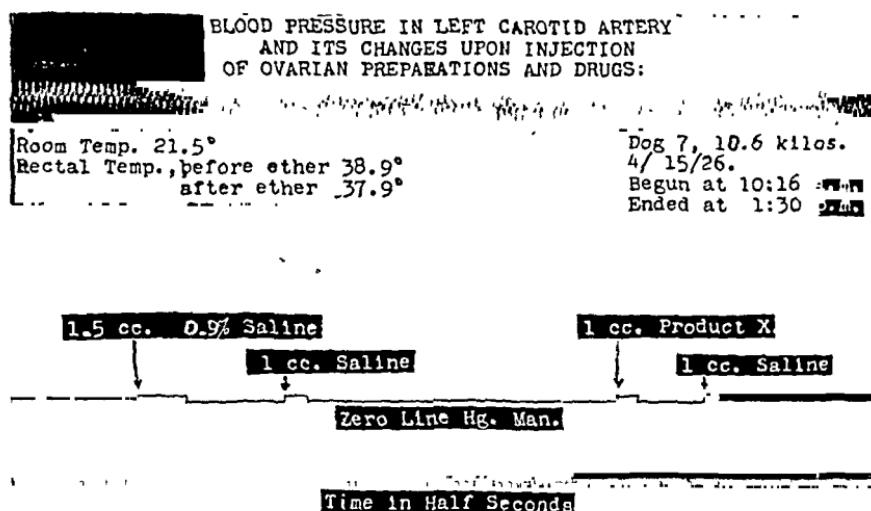


Fig. 1a. Blood pressure in left carotid artery and its changes upon injection of ovarian preparations and drugs.

of material. At least twice per week an ampoule will be tested for potency. By using this procedure failure to attain clinical results cannot be ascribed to a possible unknown deterioration of the extract.

5. *Effect of Injections of the Hormone upon Blood Pressure.* As tissue extracts frequently produce changes of blood pressure, it was deemed advisable to determine whether purified preparations of the hormone had any such effect. Of course, we still do not have the pure hormone, so that we cannot interpret our results with certainty, but one of our preparations has been purified to such an extent that we feel that a report of its effect upon blood pressure is worth while.

Cannulas were inserted in the carotid artery and femoral vein of dogs under ether anaesthesia. The blood pressure was recorded with a mercury manometer whose connecting tubing was filled with

a 5 per cent solution of sodium citrate. Time was recorded in half seconds and a signal magnet used for recording the time of injections also traced the zero line of pressure. The solutions tested were injected into a short rubber tube attached to a cannula in the femoral vein and then washed out of the cannula with 1 cc. of normal saline solution. The solutions tested were: normal saline; an aqueous suspension of 10f which was one of our purified preparations; an aqueous solution of one of our crude products; an aqueous suspension, product x, prepared by a pharmaceutical house; and an olive oil solution, product y, prepared by another company.

EFFECT OF A PURE PRODUCT  
 Dog 7 Tracing Two  
 Rectal Temp 38.5°.

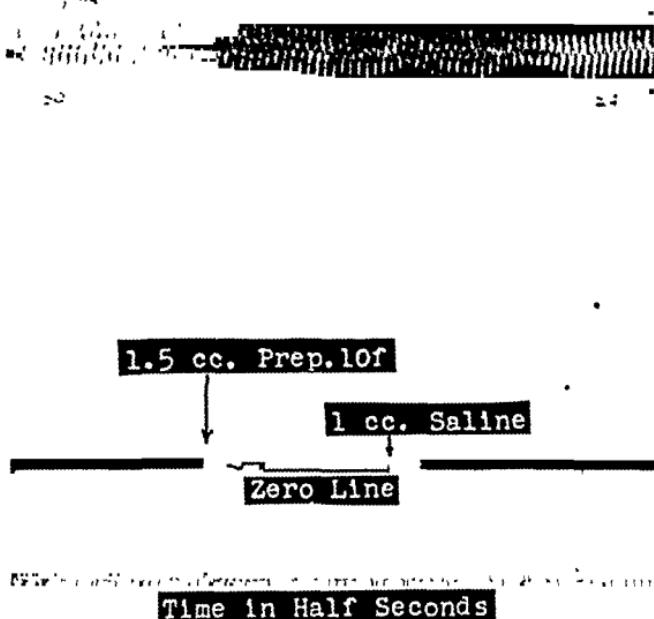


Fig. 1b. Effect of pure product.

Comparing the mean blood pressure and the heart rate (counted for 10 sec. periods) of Fig. 1a it may be seen that the pressure was 126 mm. and the rate 168. After the injection of 1.5 cc. and 1cc. of 0.9 percent saline, the values were 126 mm. and 180; and following the introduction of 1 cc. of product x,

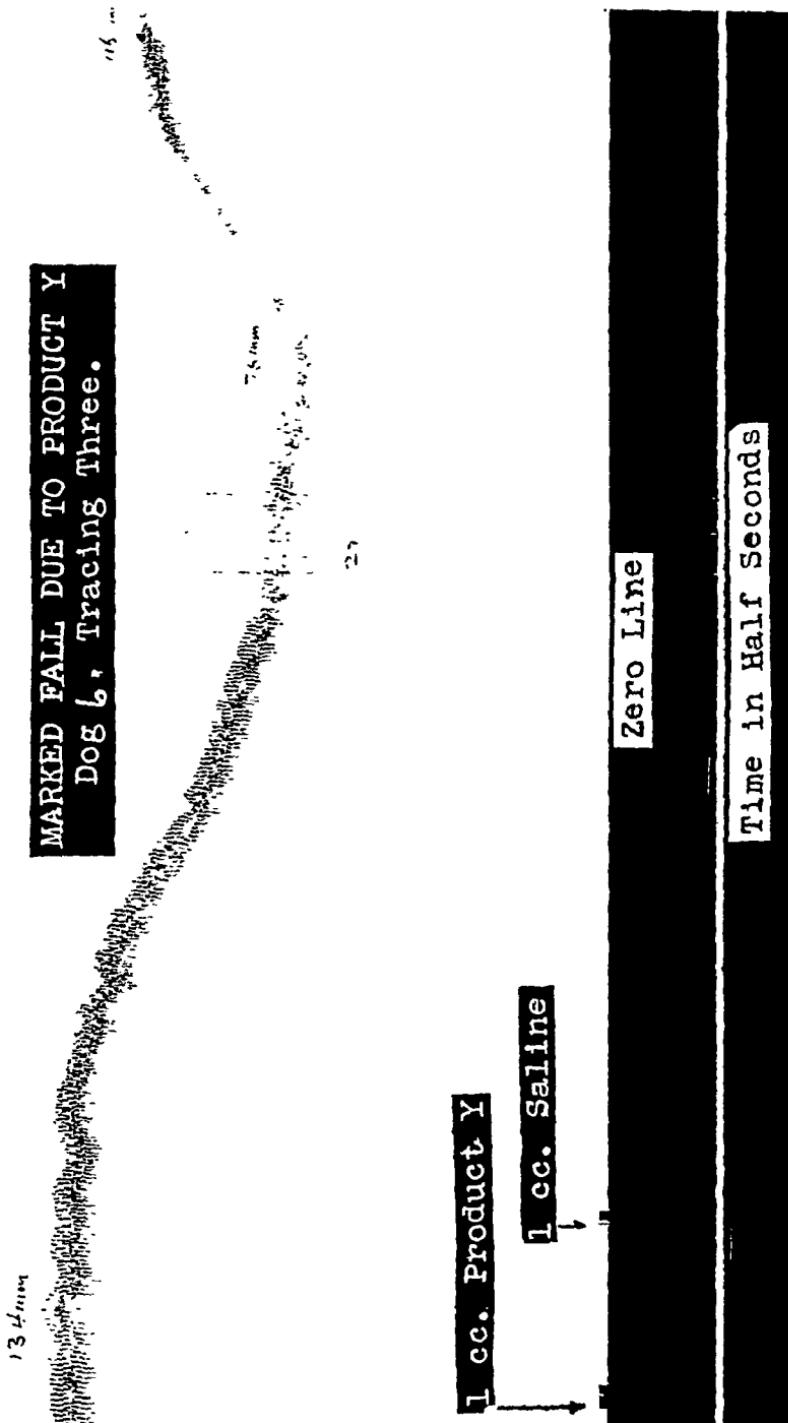


Fig. 1c. Marked fall due to product Y.

which contained 10 rat units, the blood pressure was 126 and the rate 174 per minute.

Figure 1b is a record of the effect of injection of 1.5 cc. of 10f containing 6 rat units. Blood pressure: before, 127 mm.; after, 127 mm. Heart rate: before, 180; after, 174.

Figure 1c shows the result of injecting 1 cc. of product y

DUE TO AN IMPURE PRODUCT  
Dog 7. Tracing Two.

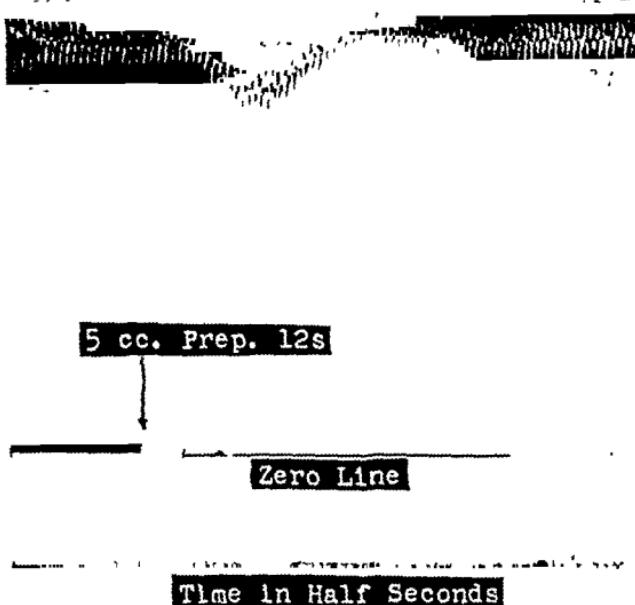


Fig. 1d. Fall due to an impure product.

which contained 5 rat units. The blood pressure at the time of injection was 134 mm. and the rate 156; after 4 minutes, during which a slow fall of blood pressure occurred, these values were 76 and 162 respectively. Shortly thereafter the blood pressure began to rise, and within 2 minutes had risen to 116 mm.

Figure 1d is a graphic record of the effect produced by the injection of 5 cc. of a crude solution of the hormone prepared from liquor folliculi. The mean blood pressure fell rapidly from 126 mm. to 110 mm., but recovered promptly.

Our results upon the effect of purified preparations of the hormone agree with those obtained by Dr. C. M. Gruber working with Allen and Doisy during the summer of 1923, in which only preliminary tests of relatively crude products were made, and with those recently reported by Laqueur and his coworkers (1926) using their own purified product made by a different method. It seems probable then that the hormone has no effect upon blood pressure and that preparations should therefore be tested upon the blood pressure before being used for experimental clinical work.

#### SUMMARY

1. A simple method of preparing potent preparations of hormone from liquor folliculi is briefly described.
2. Some of the chemical and physiological properties of this hormone are discussed.
3. The requirements that a preparation for experimental clinical work should meet are suggested.

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STUDIES ON VIGOR. VIII. THE EFFECT OF SUB-CUTANEOUS INJECTION OF CORPUS LUTEUM EXTRACT ON VOLUNTARY ACTIVITY IN THE FEMALE ALBINO RAT.

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Although the sterilizing effect of corpus luteum extracts has been shown by Haberlandt (1), Knaus (2), and Papanicolaon (3), how the active principle produces its effect has not been made clear. The correspondence between the sex cycle and voluntary activity as described by Wang (4), and Slonaker (5) in the white rat suggest the possibility of throwing some light on the question by observing what effect such extracts exert upon this activity. Presumably any positive effect observed would be ascribable to an influence of the corpus luteum upon the ovarian follicular development.

For this experiment thirty-eight rats were placed in recording activity cages (6) for "typing" when about seven months old. Within a few days they began to manifest the usual oestrual variation in activity, becoming much more active every fourth or fifth day. Fig. 1. After typing, fifteen were selected for the corpus luteum treatment and nine generally from corresponding litters for controls, the former group being somewhat the more active.

An aqueous extract of corpus luteum, excepting on one day, that prepared by Hynson, Westcott and Dunning, was then injected subcutaneously on alternate days in the amount of 0.2 cc. to each rat over a period of twenty days. The next two injections were of 0.4 cc. each, then three of 0.3 cc. each and for the remainder of the experiment 0.2 cc. each time. The treatment was discontinued after 37 days. During the last twelve days daily microscopic examinations of the vaginal secretion were made as a check on the wheel records. These revealed the same incidence between "heat" and high activity in the treated animals as in the controls. Although the graph

has in the forty days of preliminary recording a few secondary peaks, simultaneous "smear" and activity records made on a considerable number of animals in this laboratory show that these are not all due to estrus.

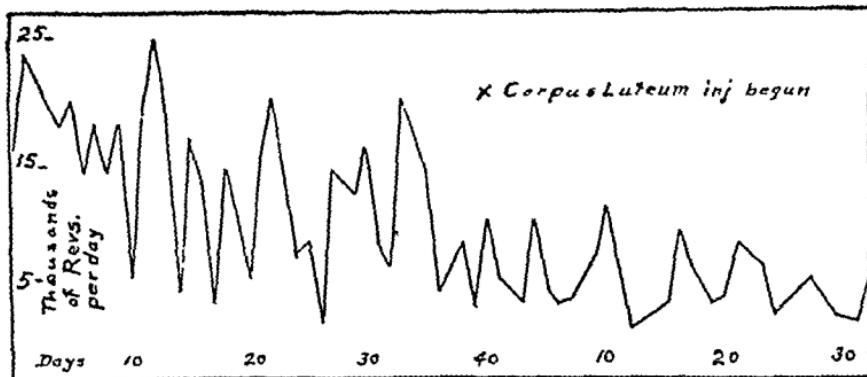


Fig. 1. Graph of cyclic activity of female white rat. The ordinates represent thousands of revolutions per day. The character x indicates when corpus luteum treatment began

The results of the experiment are considered under two heads, periodicity of activity and average daily activity. Fig. 1 is a graph of the daily activity of an animal fairly typical as to both features. As will be readily seen, the oestral variation in activity during the treatment with luteal extract does not significantly differ from that previous to treatment. This fact is also shown in table 1, which gives the average length of estrus cycle in each rat before and during the treatment, the averages

TABLE 1

Rat No.	A	B	Rat No.	A	B	Rat No.	A	B
1164	4.1	4.0	1095	4.5	4.8	1167	4.0	4.0
1077	4.4	4.3	1096	4.0	5.4	3268	4.1	4.6
1125	5.7	5.4	1100	5.0	4.0	3269	5.2	4.7
1091	4.1	4.7	1196	5.1	4.9	1110	4.8	6.0
1093	5.0	4.7	1128	4.1	4.0	1181	4.3	4.4

Table 1, showing average length of estrous cycle for each rat for 70 days before (column A) and 37 days during (column B) the treatment with corpus luteum extract. The average for the entire group of fifteen was 4.5 days before and 4.6 days during treatment.

for the entire group being 4.5 and 4.6 days, respectively. Composite graphs of each entire group were made by calculating the average daily activity over ten day periods. Table 2 gives these

averages for each animal and for each group, the latter being represented by Fig. 2. It will be seen that the activity of both groups was falling off about equally previous to the beginning of the corpus luteum injection, which was begun on March 4th.

TABLE 2

## EXPERIMENTAL GROUP

Rat No.	40 days before the treatment with corpus luteum extract was begun				30 days of corpus luteum treatment		
1077	14400	16150	8050	11450	7000	5500	2150
1091	8100	6000	6150	6300	4250	4800	2500
1093	7150	5800	5700	4500	2400	3150	2000
1095	6600	4650	5850	3700	2250	3600	2300
1096	15950	12900	14800	9200	5750	4350	4300
1100	11850	7450	6000	8000	6550	7000	7500
1110	6600	4500	3500	2400	4300	3350	4700
1125	14250	12500	9250	7400	8450	6650	5050
1128	8150	5650	3950	4050	3900	4500	4400
1164	14450	9000	4000	6250	4300	7150	4100
1166	7100	8400	5200	6800	5200	5050	3000
1167	9100	9650	6900	5050	5700	6250	5050
1181	19350	14000	7750	9000	7200	9700	9750
3268	10250	11950	12600	9700	10250	8350	6250
3269	4000	9450	10400	8000	7700	6950	5800
Average	10500	9200	7400	6850	5700	5700	4550

## CONTROL GROUP

1079	9900	7400	2700	2000	7000	7750	6000
1092	4550	4450	5900	2900	3950	4200	1400
1101	3250	3800	1700	2600	3300	3100	1650
1115	10000	8350	8050	6150	8150	6650	6500
1173	1700	950	750	1000	1500	1400	1000
1180	2050	1800	1100	1300	1000	1200	1250
1182	16600	16700	9600	4250	4450	1750	3500
1183	14150	15700	13650	10150	8400	7900	3550
3270	6400	6200	8700	10200	5800	8750	8950
Average	7600	7200	5800	4500	4800	4700	3700

Table 2, showing the average daily activity of each animal reckoned by ten-day periods. Also the average for each group.

At this point the controls show an increase, a thing to be expected at this time of year, according to our experience. For the first ten days after the beginning of the treatment the activity of the experimental group fell off, but thereafter it remained on a par with the controls. The fact that the cyclic character of the activity was unaffected by the corpus luteum leads to the belief that the diminished total activity for the first few days was due to some other cause, possibly soreness produced by introducing the hypodermic needle repeatedly into the skin of the inguinal region. Some other unknown factor was doubtless in

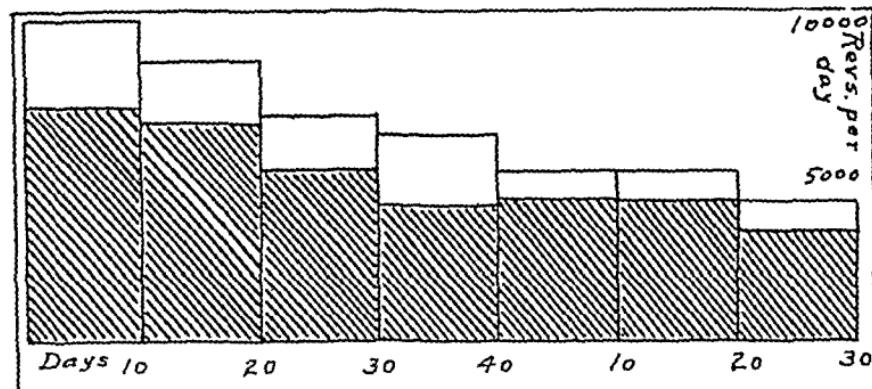


Fig. 2. The entire vertical rectangles, shaded and unshaded portions together, represent the total average activity of all of the treated animals for each of the respective ten-day periods. The shaded portions represent the activity of the controls.

part responsible for this condition, an examination of the individual activity records, not given in this paper for want of space, revealing that four of the fifteen subjects fell off extraordinarily in activity three or four days before the injections began and had not yet recovered their usual activity at that time. This fact, incidentally, does not vitiate the experiment because the periodicity of the activity was the main point at issue.

It is evident, then, that within the period of treatment and with the amount of extract used, and this was seemingly comparable to the amounts sufficient to produce sterility in experiments reported by other workers, the voluntary activity is unaffected. As bearing on this question, Knaus (2) has reported sterility which was only temporary, and that during continuance of the treatment pregnancies ultimately occurred which

resulted in unusually large litters. From this he infers that not development of ova but ovulation was for a time suppressed. Accepting the view of Allen and Doisy (8) that the female hormone is produced by the follicle cells under the influence of maturing ova, it is apparent that if the cyclic increase of activity is among the phenomena dependent upon the periodically secreted follicular hormone then under the conditions of this present experiment the luteal extract has not been antagonistic, at least in amount, to the follicular secretion proper, that is, the sex-hormone so-called. This view would not be inconsistent with that of Knaus referred to above. Papanicolaou (3) in a report published since the completion of this experiment states that (in the guinea pig) the full growth of the follicles and the process of ovulation are suppressed by the specific luteal hormone. Our results are not inconsistent with this view, especially the latter feature. They indicate, however, that although ovulation may not have occurred as usual, ova have been developing at the usual times, as shown by the continuance, throughout the period of treatment, of cyclic activity variations, and vaginal changes corresponding to the oestral cycle. In a word, corpus luteum extract antagonizes ovulation, but does not prevent the development of ova.

#### SUMMARY

In an experiment with nine control white rats and fifteen others treated by subcutaneous injections of aqueous extract of corpus luteum over a period of thirty-seven days, the voluntary activity of the animals was unaffected in periodicity and total amount. Corpus luteum, therefore (assuming a potency of the extract used), does not prevent the formation of follicular hormone.

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THE EFFECT OF FOLLICULAR AND PLACENTAL HORMONES UPON THE MAMMARY GLANDS AND GENITAL TRACT OF THE OPOSSUM.

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It has been abundantly demonstrated in the last few years that the ovarian follicular hormone extracted by lipoid solvents from the liquor folliculi or similar extracts from the placenta\* are capable of stimulating the genital tracts of immature or spayed adult female mammals.† The effect upon the mammary glands of such experimental animals has also been stated to be positive, but most authors refer to the mammary glands incidently and more or less casually, devoting chief attention to the size and vascularity of the uterus (Ascher and Grigoriu, 1911; Fellner, 1913, 1923; Iscovesco, 1914; Hermann, 1915). Vintemberger (1924) reports a well-executed set of experiments in which he induced an oestrous growth in the mammary glands of immature female and adult male rabbits by

\*The name of Halban (1905) is especially associated with the theory of the placental hormone as the chief stimulus for the proliferation of the mammary gland during pregnancy. The theory, as stated by him, does not, however, deny the action of the ovary in the early part of pregnancy; the action of ovarian hormones in the early part of pregnancy is conceded.

†In a recent contribution Loewe (1925) has pointed out the superiority, in point of accuracy and definiteness, of the method of Allen and Dolsy (1923), in which castrated mice or rats are used as test animals and the cornification of the vagina constitutes a positive result. Loewe generously states the method as being more accurate than his own, in which he used the swelling of the mammary glands (Hypermastie) as the diagnostic sign. See also Courrier (1925), Zondek and Aschheim (1925, 1926), Frank and Gustavson (1923).

means of intraperitoneal injections of crude bovine follicular fluid. §

For an experiment of this kind the opossum seemed to us to be well adapted, by virtue of the concentration of mammary glands in the limited area of the pouch and the fact that consequently, as Hartman (1923) has shown, changes in thickness in the gland are readily detectable, after some practice, by palpation. The same writer also showed, on anatomical grounds, that the mammary glands begin their growth under the influence of the growing Graafian follicles. It therefore seemed reasonable to suppose that, since in the opossum the mammary glands must needs be ready for lactation at a very early date (13 days or less after fertilization!), they might be unusually responsive to this hormone. At the same time the low position of the opossum in the mammalian series seemed to offer a further opportunity to test the species non-specificity of this hormone secured from man and other Eutheria (Cf Allen, et al., 1924).

The experimental animals were all mature female opossums one, two, or more years old. All were castrated and the mammary glands allowed to involute until the glandular substance was no longer palpable, that is, until the skin containing the involuted glands had become as thin as skin elsewhere on the body. This condition is designated as "zero" in the protocols †. Growth in thickness or changes in turgescence of the glands were noted by palpation, and at frequent intervals vaginal smears were made by the Stockard and Papanicolaou

§The crude follicular fluid was employed by Sonnenberg (1907), Frank (1922) and others and the crude "Press saft" of organs was originally used almost exclusively. But it is desirable to avoid injection of toxic substances contained in so complex a mixture by precipitation of the toxic substances of the juice by means of (inert) solvents alcohol acetone and ether. This is accomplished in the method of Allen and Doisy which follows in part the suggestive work of Icconi, Isovesco and Heimann. Recently, Ralls, Jordan, and Doisy (1926) have worked out a simplification of the technique.

\*The same conclusion had been reached in this manner by Robinson (1918) in his study of the oestrous phenomena of the ferret. Iob and Hesselberg reported an initial but transient hypertrophy of the mammary gland in the guinea pig which they attributed to the Graafian follicles. Bucuita (1909), through a prior reasoning attributed the development of the secondary sex characters as well as oestrus to the follicle perhaps the liquor folliculi itself, a conclusion which he suggested should be determined by experiment. The answer has now been definitely given by Allen and Doisy (1923).

†The ideal conditions for the experiment would have been to secure animals in anoestrus or the testing condition of December and early January, when the reproductive organs are considerably involuted to begin with. But it was impracticable to begin collecting the animals until the end of January when most of them were pregnant or had young pouch young. Time then had to be allowed for complete involution to take place maturation being the guide, according to the method referred to above (Hartman, 1919).

method, for in the opossum as in rodents, the histological condition of the vagina is a certain index to the changes in the uterus as well as the mammary glands, all standing in correlation to one another and to the ovary (Hartman, 1919). After autopsy the organs were fixed, imbedded, and for the most part sectioned and studied microscopically to determine the extent of regeneration effected or to observe the process in progress, as shown by mitotic cell division.

A word must be said about the vaginal smear in the majority of cases. In only two (Nos. 977 and 1000) was a typical clear-cut oestrous cornification of the vaginal mucosa obtained, with the almost complete disappearance of leucocytes and epithelial cells. In all other cases the latter never disappeared, although in all subjects cornification proceeded to a varying extent, perhaps more in one part of the organ than another (Hill and Fraser, 1925). Just such admixture of cells, giving an "atypical" picture to the vaginal smear, are quite common in animals experiencing abortive attempts at oestrous because of atresia of the graafian follicles (Hartman, 1924). Frank and Gustavson (1925, p. 6) doubtless had the same picture before them when they wrote: "Intermediate and partial reactions may occur." Such partial cornification will be referred to below as "atypical."

Two series of experiments were made. In six cases placental hormone, in five cases follicular hormone, was used. The hormone in all cases was prepared by Dr. Allen according to the method of Allen and Doisy and standardized in terms of rat units (Allen et al., 1924; Loewe, 1925). The injections were made twice daily, usually beginning with 0.5 cc. of the oil and increasing to 0.75 cc., 1.0 cc. and 1.5 cc. twice daily. In the notes the total amount injected over a period of days is recorded.

The essential details of the experiments are briefly stated in the following protocols.

#### PROTOCOLS

##### SERIES I. INJECTION OF PLACENTAL EXTRACT

No. 979, 1320 g. Feb. 11, both ovaries and uteri removed.  
Pouch young had been lost some time preceding operation.

March 3, mammary gland very thin, practically zero.

March 3 to 10 (20 days after operation), 9.0 cc. of placental hormone I injected (36 rat units).

March 9, mammary gland "thicker"; March 11, "decidedly thicker." Vaginal smear atypical, near-oestrous in character.

March 12, animal died. Organs considerably increased above castrate condition, but a great deal less than at normal oestrus.

No. 984, 885 g. (small). Ovaries removed Feb. 17. Pouch young had been lost some time before operation.

March 3-5, mammary glands almost zero.

March 5-9 (16 days after operation), 6.5 cc. placental hormone II injected (26 rat units).

March 9, mammary gland "rather thick"; March 10, "distinctly thick."

Mammary gland uniformly thickened. In section numerous thick-walled, regenerated alveoli with an occasional mitosis can be seen budding off of the more dilated, thin-walled alveoli of the previous lactation.

Uterus, vagina, and lateral vaginal canals enlarged and vascular, as in pro-oestrus. Uterus has well-preserved mucosa, including thickened epithelium and regenerated, rather closely packed glands, showing an occasional mitosis.

The growth changes in this experiment were carried well towards the oestrous condition.

No. 977. Pouch young removed February 19 and double ovarieotomy performed.

March 10, mammary glands thin.

March 16-25 (25 days after operation), 16.75 cc. of placental hormone III injected (67 rat units).

March 21, mammary gland "thicker"; March 22, "clearly thicker"; cornified cells in vaginal smear.

March 23, killed.

Mammary glands very thick, as in pseudo-pregnancy of several days' standing (thicker than at normal oestrus). In section glands are seen to be well lobulated, each lobule consisting of numerous moderately dilated acini; mitoses numerous.

Uterus at least as at oestrus; vascular, round, and turgid; glands greatly convoluted; mitoses moderately numerous.

Vagina greatly hypertrophied; mucosa at end of post-oestrous desquamation; much cornified material in lumen; beginning of leucocytosis.

Lateral vaginal canals collapsed, as normally in metoestrus, giving evidence of previous great dilatation.

Altogether, the reproductive organs present the picture of an animal well advanced in the pseudo-pregnant condition.

No. 981. Embryos near term February 16; both ovaries and both uteri removed. February 24, mammary gland involuted, thus: March 3, "just palpable." March 9, 16, 19, "very thin."

March 27-31 (39 days after operation), injected 6.0 cc. (24 rat units) or the remaining portion of placental hormone III (partly used on No. 977).

April 1, mammary gland decidedly thicker. Vaginal smear "atypical" oestrous type.

April 3, glands thick and firm, as in late pro-oestrus.

April 7, killed. Organs again greatly though not completely involuted, autopsy having been made 7 days after discontinuing the injections.

No. 998(a), 2000 g. Pouch young removed and female ovariectomized February 27.

March 21 (22 days after operation), mammary glands zero.

March 21-28 (interval 24 days), 15.25 cc. placental hormone IV injected. No effect whatever was noted, either in the vaginal smear or on the mammary glands. The results being clearly negative, the animal was kept for another experiment (v.i.),

The hormone here used was extracted from a human placenta which had inadvertently stood in the warm sun for a whole day. Putrefactive agents or autolysis or both had doubtless rendered the hormone inert.

No. 1000. Trapped at Columbia, Mo., and ovariectomized on February 4.

February 25 to March 5, 17.0 cc. of placental hormone V were injected (69 rat units).

Mammary gland very thick, as in early pseudo-pregnancy. Considerable development of new alveoli, moderately dilated, mostly one-layered; mitoses numerous.

Vagina greatly enlarged, almost maximal, as at oestrous; desquamation of cornified layer almost completed. Moderate leucocytosis of vaginal epithelium.

Lateral vaginal canals give every appearance of collapse after great oestrous dilatation.

In this experiment the hormone action clearly resulted in growth and hypertrophy of the organs to a degree normally found in early pseudo-pregnancy.

#### SERIES II. INJECTION OF FOLLICULAR EXTRACT

No. 957, 1118 g. Ovariectomized January 21 while in anoestrus; one ovary transplanted in pieces into a rectus abdominis muscle. January 27, no change in mammary gland. Escaped end of January; accidentally recaptured March 23. April 3, mammary glands reported in cage notes as temporarily somewhat thickened; vaginal smear, however, showed no cornified cells. No further sign of sexual activity whatever.

May 11 to 16 (110 days after operation), 6.25 cc. of follicular hormone injected (18.75 rat units).

May 17, atypical pro-oestrous smear. Killed May 19. Mammary gland somewhat thickened.

Uterus as in early pseudo-pregnancy; mitoses very numerous in greatly convoluted glands, which are well ciliated.

Vagina in later stage of cornification with great infiltration of leucocytes, as in metoestrus.

This experiment may have been complicated by the possible influence of the transplant, which, however, could not be found at autopsy.

No. 982. Pouch young 5 or 6 days old; removed, and female ovariectomized February 17.

March 27. Mammary glands zero.

May 11 to 16 (93 days after operation), 9.25 cc. follicular hormone injected (18.5 rat units).

May 17. Vaginal smear oestrous, atypical. No proliferation of mammary gland, only congestion and some extravasation. No other record made.

No. 958. Oestrus January 27; February 11. dioestrus.

February 22. Ovariectomy; mammary gland nearly zero.

May 21 to 26 (88 days after operation), 14.5 cc. follicular hormone injected (43.5 rat units).

May 29, killed. Mammary gland slightly thickened, firm. Uterus as in early pro-oestrum. Lateral vaginal canals slightly, median vagina, considerably enlarged; vaginal smear pro-oestrous, atypical.

This experiment resulted in a correction of the castration atrophy of three months' standing, but failed to advance the organs beyond the early pro-oestrous condition.

No. 987, 1116 g. Si., pouch young, 10 days old, removed and female ovariectomized February 20.

May 21 to 31 (96 days after operation), 32.0 cc. follicular hormone injected (96 rat units).

June 1, killed. Vaginal smear more or less as at oestrus, but atypical. Vagina and ateral vaginal canals about as in dioestrus; uteri and mammary glands developed to the normal oestrous stage.

A large quantity of hormone was used in this experiment. The subject recovered thoroughly from its profound castration atrophy. Uteri and mammary glands had developed well towards the oestrous condition, but the vagia and the lateral vaginal canals, normally the first to respond, remained the most refractory.

No. 993(b), 2000 g. (very large). This animal had received placental hormone IV (v.s.) without effect March 21 to 28.

May 23 to 29 (85 days after operation), 18.0 cc. (90 rat units) follicular hormone injected. Killed 4 days later.

Mammary glands slightly thickened; regeneration of alveoli, numerous mitoses. Genital tract recovered from castration atrophy of preceding months, but only slightly advanced towards oestrous condition.

## DISCUSSION OF RESULTS

It is seen from these experiments that in all cases but one (No. 993, first injection), the hormone stimulated the growth of the mammary glands and the genital tract and corrected the atrophy to which these organs are always subjected after ovariectomy. In certain cases, especially in Series II, this is as much as can be said for the action of the hormone; but in others, notably in No. 997 and No. 1000, of Series I, not only were the phenomena of oestrous pronounced and quite typical, but the organs went farther and exhibited distinct symptoms of pseudo-pregnancy. This holds especially for the mammary

TABLE 1  
*Giving Summary of Data Presented in the Protocols*  
 SERIES I: PLACENTAL EXTRACT

No. of animal	Date of		Time interval (days)	Amount injected (cc.)	Rat units	Results
	Castration	Injection				
979	Feb. 11	Mar. 3-10	20	9.0	36	Fair
984	Feb. 17	Mar. 5-9	16	6.5	26	Very good
977	Feb. 19	Mar. 16-25	25	16.75	67	"Pseudopregnant"
981	Feb. 16	Mar. 27-31	39	6.0	24	Fair
993	Feb. 27	Mar. 21-28	22	15.25	0	Negative
1000	Feb. 4	Feb. 25- Mar. 5	21	17.0	69	"Pseudopregnant"

## SERIES II: FOLLICULAR EXTRACT

957	Jan. 21	May 11-16	110	6.25	18.75	Good
982	Feb. 27	May 11-16	73	9.25	18.5	Poor
958	Feb. 22	May 21-26	88	14.5	43.5	Fair
987	Feb. 20	May 21-31	90	32.0	96.0	Fair
993	Feb. 27	May 23	85	18.0	90.0	Good

gland, but is also true to a large degree of the genital tract as well.

The hormones from both sources (human placenta, pig's graafian follicles) thus had the expected effect. However, it was somewhat surprising, in view of former work on the rat, that the extract of human placenta should turn out to be so much more potent than the extract of the pig follicular fluid.

The explanation of this discrepancy, if such it is, lies, it seems to us, in the extent of castration atrophy attained by the organs in the two series, much more profound in the second series, which proved to be the more refractory. In this series 110, 73, 88, 90, and 85 days, respectively, elapsed between the removal of the ovaries and beginning of the injections, against 20, 16, 25, 39, 22, and 21 days for the first series (Table 1). It is a well-known fact, holding true for the opossum as well as for the classical experimental mammals and man, that time is the determining factor in the extent of castration atrophy. Gynecologists are furthermore well aware of the refractory nature of the hyperinvolved puerperal uterus which sometimes accompanies lactation. This condition and other forms of amenorrhea are doubtless due to ovarian insufficiency, as has been suggested by various gynecologists (e. g., Novak and Graff, 1921; Guggisberg, 1925). The symptoms in such cases simulate those of complete castration. Any one who has had any considerable experience with experimental mammals knows the almost invariable correlation between atrophy of the genital tract and mammary gland and hypotypical ovaries.

Guggisberg (1925) offers a somewhat different explanation to the refractiveness of the uterus after a lapse of time. He contends that the sensitization of the uterus by the ovary is prerequisite (he reports almost no effect on the mammary glands in any case). This effect wears off more and more after castration, until the uterus becomes permanently refractory. As a matter of fact, Guggisberg states that, for obscure reasons, a considerable percentage of animals fail to react, whether castrated or not.

The two series of experiments presented are, therefore, not strictly comparable. Whether the factor of time, as set forth above, is the true explanation of the differences in results attained must be left for further experimentation. The matter is of considerable importance if the method is to be used in the standardization of the hormone.

As a further result of the foregoing experiments, the species non-specificity of the sex hormone is thus extended to the marsupial: extracts of human placenta and pig's liquor folliculi are found effective on the reproductive organs of a representa-

tive of the lowest class of mammal having an intrauterine gestation. This result is, of course, not surprising, if one consider that the ovaries of birds (Allen, et al., 1924) and fishes (Fellner, 1925) furnish the hormone in question. It would seem probable, therefore, that this ovarian hormone consists of a definite compound, or at least a common organic radicle, widely distributed in the animal series. In this sense this hypothetical body is comparable to such fundamental chemical entities as adrenalin, insulin, and iodothyronin (thyroxin), which are widely distributed.

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# EPHEDRIN THERAPY IN ADDISON'S DISEASE \*

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Our knowledge of Ma Huang, according to Chen, dates back into the dim history of China some 5,000 years. "Ma" signifies astringent, and "Huang" yellow. The first mention of it appeared in the Chinese dispensatory in 1596 A.D. Nagai, in 1887, isolated an alkaloid from it which he named ephedrin. The recent work of Chen and Schmidt has focused attention on the pharmacologic actions of ephedrin and its possible clinical value.

The chemical structure of ephedrin, according to Chen, is probably  $C_6H_5OH \cdot CH_2CH_3 \cdot NHCH_3$ . Kendall, of the Mayo Clinic, has investigated the fundamental behavior of ephedrin and epinephrin, particularly in relation to their oxidizing properties. In this connection we quote him as follows:

"The structural formula of epinephrin has been established by its synthesis. The chemical groups present and their precise arrangement are known beyond question. The chemical structure of ephedrin is also known, and inspection of the structural formulas of these two substances show them to be closely related. The activity of each is bound up in the actively functioning groups which probably are the methylamin group in ephedrin. The difference in the physiologic activity of these two substances lies in the presence of the two hydroxyl groups in the benzene ring of epinephrin. These two groups which are adjacent carry with them the assurance of the short time for activity of the molecule, because through these groups the molecule is easily destroyed. The benzene ring in ephedrin is unsubstituted, and in vivo and in vitro experiments show that the molecule is very much more stable than is epinephrin. Epineph-

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rin is oxidized comparatively easily, owing to the presence of the two hydroxyl groups of the benzene ring. Ephedrin is stable towards oxidizing agents. Physiologic experiments have shown that epinephrin functions almost instantly and its action is over within a few minutes, but the effect of ephedrin lasts for several hours. The physiologic dose of epinephrin is measured in tenths of milligrams and the physiologic dose of ephedrin is many times as great."

The pharmacologic action of ephedrin has been carefully investigated by Amatsu, Kubato, Chen and Schmidt. In experimental animals, dogs, cats and rabbits, ephedrin has an effect on smooth muscle, on secretion, and on the circulation, indicating sympathetic stimulation similar to that of epinephrin. There is a prolonged rise of blood pressure with cardiac acceleration and frequently vasoconstriction. The heart effects are evinced by increased rate and strength of contraction which is not inhibited by atropin or by sectioning the vagi. Repeated injections in the animal cause a lowering of blood pressure. Chen's investigation indicates that ephedrin produces a stimulation of the accelerator ganglia of the heart and the accelerator nerve endings and depression of the heart muscle. Its vasomotor action is due to stimulation of the vasomotor nerve endings.

The toxicity of the drug is low; 25 mg. given subcutaneously to rabbits in daily doses for four weeks is without toxic effects. The total dosage here consumed was eight times the single minimal lethal dose. No tolerance developed to the mydriatic or pressor action of the drug. No visceral damage was discovered.

Because of the epinephrin-like action and the low toxicity, Chen suggested its use in states of low blood pressure, shock and hemorrhage, in Addison's disease and other types of hypotension. Because of its localized vasoconstrictor action on the nasal mucous membrane, attention was called to its possible usefulness in this field. The outstanding advantages of ephedrin, as compared to epinephrin, are its more prolonged action and its effectiveness when given orally. Miller has reported the results obtained by the use of ephedrin in a group of eighty cases representing various pathologic conditions. No significant toxic effects were observed when doses of from 50 to 125 mg. were given by mouth or subcutaneously. In a large majority of the cases there was some elevation of blood pressure. In 20 per

cent the increase was 40 mm. of mercury or more. The increased pressure was maintained for from three to eight hours. In two cases of Addison's disease there was some symptomatic improvement. Relief was obtained in the attacks of bronchial asthma, and temporary improvement was noted in a case of circulatory collapse. An increase of the basal metabolic rate was observed in two cases. Miller states that the minimal lethal dose of ephedrin is from thirty to one hundred times that required to produce physiologic effects.

In the Mayo Clinic the drug has been used in several different connections. Gaarde and Maytum report that in twenty-six cases of active ragweed fever, treated daily with ephedrin (65 mg. capsules), one-half of the patients obtained almost complete relief for from three to seven hours following each administration. In seven cases there was no effect, and four patients had but moderate relief. On the other hand, their results in a limited study of bronchial asthma were not so satisfactory. In treating the nose and throat, Hempstead has used ephedrin for constriction of the nasopharyngeal mucous membrane and finds that its effect persists much longer than that of epinephrin, and is not followed by the compensatory dilatation so often seen when epinephrin is used. He has also used it in combination with local anesthetics in tonsillectomy. While he has not yet worked out to his entire satisfaction the exact equivalent dosage, he believes that ephedrin promises relief from the dilatation and subsequent bleeding, which has been a considerable menace when epinephrin has been employed.

Our studies cover the use of the drug in a series of twenty-eight cases: fourteen of Addison's disease, two of questionable Addison's disease, a control group of nine cases of hypotension, two cases of pituitary tumor, and one case of endocrine obesity. Fourteen patients presenting the classical picture of Addison's disease were treated in the hospital. Three were given a daily dose of from 50 to 250 mg. of ephedrin for prolonged periods of time, either with or without the Muirhead regimen. The blood pressure was taken twice daily. In three cases repeated tests with ephedrin were made in which a single dose of 50 or 70 mg. was given orally under basal resting conditions; the blood pressure and pulse rate were taken at half-hour intervals

for a period of three or four hours. Eight patients were given one or more doses of 50 or 70 mg. of ephedrin, but the blood pressure and pulse rate were not followed systematically. Three patients, during the administration of the Muirhead treatment, were observed in the shock-like condition which occurs at times in the decompensated stages of Addison's disease; they were given ephedrin in the hope of tiding over a crisis. In addition, two questionable cases of Addison's disease, with mild generalized pigmentation, low blood pressure and weakness, were given ascending doses of ephedrin, up to a maximal dose of 300 mg., without toxic effects.

The calorigenic action of ephedrin was studied in three cases of Addison's disease.\* From 50 to 100 mg. of ephedrin was given orally, and the basal metabolic rate was determined at half-hour intervals for a total of four or five determinations.

Nine cases of chronic nervous exhaustion and hypotension were used as controls, and the clinical, subjective and objective effects of ephedrin studied. Two cases of pituitary tumor with low blood pressure and low metabolic rate were treated with ephedrin and thyroid extract as a preoperative measure.

#### EFFECTS ON BLOOD PRESSURE

*Addison's Disease.* The effects of repeated increasing doses of from 25 to 100 mg. of ephedrin are shown in three cases in Table 1. In Case 1 comparative determinations were carried out with small and large doses of ephedrin and also (for a control) without the drug. With 25 mg. a demonstrable rise of 20 mm. of mercury was noted five hours later, and the elevation was maintained to some degree for a period of four hours. There was no change in the diastolic pressure. A similar test on the following day produced no changes in the blood pressure and a subsequent test with 250 mg. showed no significant effect on the blood pressure. Case 2 showed a moderate response after 60 mg. of ephedrin on two successive days. A maximal increase of 18 mm. of mercury of at least two hours' duration was noted, without significant change in the diastolic pressure. In Case 3 there was an increase in the systolic pressure of 20 mm. of mercury in one hour and fifteen minutes after the administration of from 50 to 60 mg. of the drug. The diastolic

\*This was attempted in other cases but the strain resulting from repeated breathing tests necessitated its discontinuance on several occasions

TABLE 1

*Effects of ephedrin on blood pressure in cases of Addison's disease*

Case	Date, 1925	Time	Ephedrin, mg.	Blood pressure	
				Systolic	Diastolic
1	4-29	9 00	25	92	58
		10 00		100	60
		11 00		100	60
		12 00		90	56
		1 00		100	60
		2 00		112	70
		3 00		100	60
		4 00		104	56
		5 00		98	62
		7 00		98	60
		8 00		98	56
	4-30	9 00	25	92	58
		10 00		90	60
		11 00		96	54
		12 00		82	50
		1 00		86	50
		2 00		86	50
		3 00		90	58
		4 00		92	60
		5 00		92	60
		6 00		90	60
	5-2	9 00	None	86	56
		10 00		80	58
		11 00		122	70
		12 00		88	32
		1 00		88	58
		2 00		88	56
		3 00		88	50
		4 00		90	52
		5 00		95	60
		11 00		88	54
	5-4	3 00	250	94	
		5 00		98	64
	2	15 minutes	30	Patient at rest	
		10 50		110	68
		11 35		100	70
		12 05		108	68
		1 05		106	68
		1 35		106	68
		2 05		108	66
		9 00		108	74
		9 00-9 15		Patient at rest	
		10 00		112	62
	1-11	11 00	60	118	72
		11 30		118	70
		12 00		114	66
		9 00		100	60
		9 15		100	60
		9 30		112	68
		10 00		112	68
		10 30		112	68
		11 00		112	65
		11 30		118	70
		12 00		118	70

TABLE 1 (Continued)

Case	Date, 1924	Time	Ephedrin, mg.	Blood pressure	
				Systolic	Diastolic
3	12-20	4 45	50		
		5 00		115	70
		5 35		124	58
		6 00		140	74
		6 30		140	70
		7 00		138	58
		7 30		136	52
		8 00		120	48
		8 30		110	46
		9 30		84	40
		10 00		86	40
12-21	12-21	7 20	50	100	68
		7 35		104	64
		8 05		104	59
		8 35		120	68
		8 50		116	58
		9 00		114	56
		10 00		118	60
		10 30		114	54
		12 00		106	54
		2 00		108	58
		6 00		108	58
1925 1-2	1925 1-2	10 15	60	124	58
		10 30		120	56
		10 45		142	60
		11 15		144	62
		11 45			
1-15	1-15	10 15	60	124	58
		10 30		120	56
		10 45		142	60
		11 15		114	62
		11 45			

pressure showed no significant change. Subsequent comparative tests carried out on successive days showed comparable increases in blood pressure

The effects of the prolonged administration of daily doses of from 50 to 250 mg. of ephedrin on the blood pressure in Addison's disease is shown in Figures 1, 2 and 3. The administration of ephedrin is associated with a slight rise in blood pressure (Fig. 1). The fall of pressure on the seventh day was thought to be due either to overexertion or to catharsis. Bramwell has emphasized the ill effects of catharsis. This patient confirms his observation since he himself ascribes his relapse to purgation. Figure 2 shows a sustained increase in blood pressure over a period of five days, under the influence of ephedrin. After the administration of ephedrin was stopped, the diastolic pressure decreased but the systolic pressure was sustained. The comparative effects of ephedrin and another member of the

epinephrin group are shown in this figure. Figure 3 is of unusual interest in that it depicts the increase in both systolic and diastolic pressure following the use of 250 mg. of ephedrin daily for fourteen days. Despite this increase in blood pres-

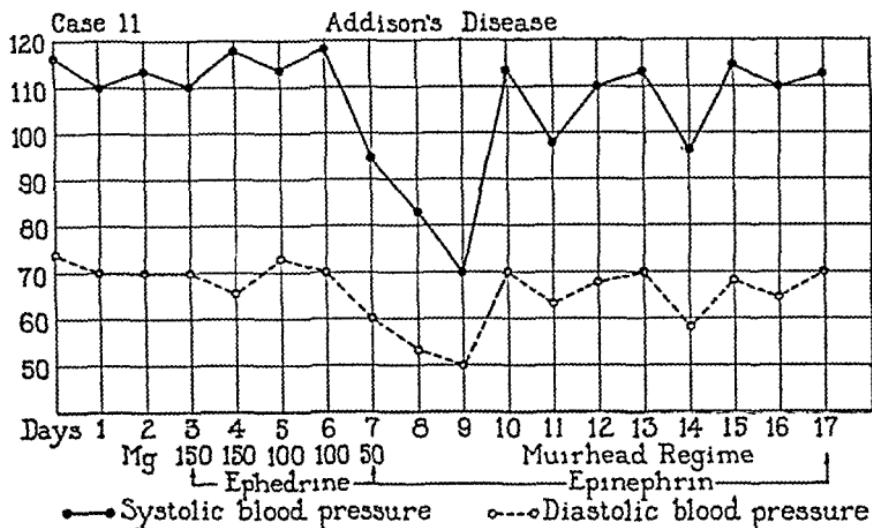


Fig. 1. A marked fall in blood pressure on the seventh day, attributed to catharsis or overexertion. The pressure had been satisfactorily sustained by ephedrin up to that time.

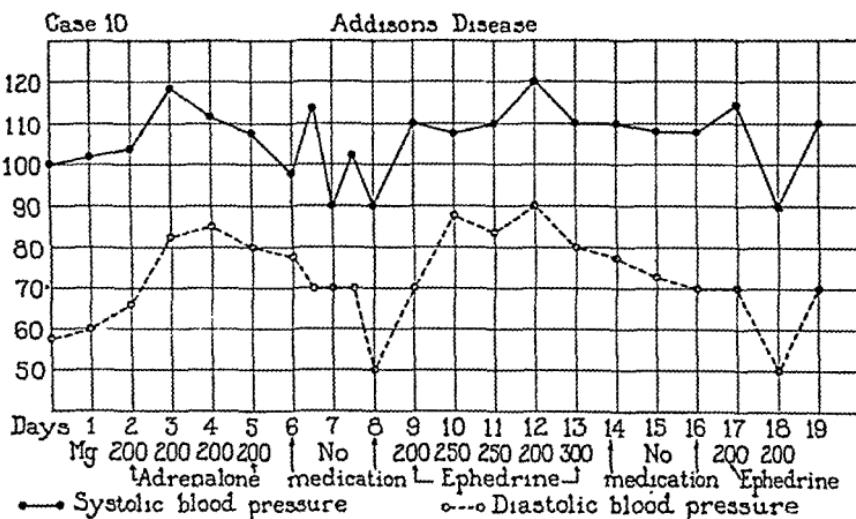


Fig. 2. A sustained increase in blood pressure over a period of five days, after the administration of ephedrin.

sure, the patient died under treatment. The final drop in blood pressure is regarded as an antemortem phenomenon.

A third group comprises eight cases of Addison's disease in which one or more doses of ephedrin were administered for

its clinical effect, but without such detailed studies of the effect on blood pressure or metabolism. Some patients in this group were under ephedrin treatment over a number of days. In three of these cases, ephedrin was employed more or less as a last resort in the effort to tide the patient through a critical period of the disease. The clinical results in advanced cases of Addison's disease were distinctly disappointing. In not a single such instance did we feel that ephedrin contributed much to the feeling of well-being or to the recovery of the patient.

In two cases of questionable Addison's disease increasing doses of ephedrin were administered up to 300 mg. a day. The effects on blood pressure were transitory and the general level

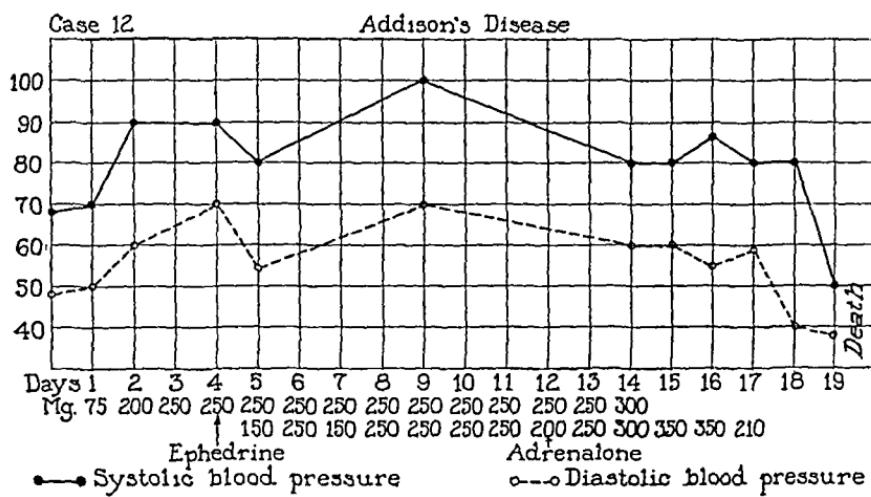


Fig. 3. An increase in both systolic and diastolic blood pressures after the daily use of ephedrin for a period of fourteen days.

of blood pressure was not significantly increased during a period of five days.

*Nervous Exhaustion and Hypotension.* The effects of ephedrin on the blood pressure in nine cases of hypotension are illustrated by typical cases in Tables 2 and 3. There were moderate increases in the systolic pressure ranging from 10 to 30 mm. of mercury. The increase in diastolic pressure was not consistent, but averaged about 11 mm. of mercury. The maximal changes in blood pressure occurred from one-half to three hours after the administration of the drug and persisted from three to six hours. Objectively, there was no other evidence of clinical improvement, although several of the patients were convinced that they felt somewhat stronger.

TABLE 2

*Effects of ephedrin on blood pressure in cases of chronic nervous exhaustion*

Case	Date, 1925	Time	Ephedrin, mg.	Blood pressure		Pulse	Remarks
				Systolic	Diastolic		
1	2-5	2 45	75	102	62		
		3 00		100	56		
		3 30		110	58		
		4 00		112	72		
		4 30		118	56		
		5 00		118	58		
		5 30		110	60		
		6 00					
	2-6	4 00	75	102	54	92	
		4 15		118	70	72	
		5 15		126	70	74	
		5 45		122	70		
		6 15		104	48	92	
		6 45		112	64		
		7 15					Weakness and trembling lasting four hours
2	2-7	12 45	75	95	55	80	
		1 00		94	58	88	
		1 30		94	62	88	
		2 00		98	60	100	
		2 30		80	45		
		3 10		94	60		
		3 30		120	60	84	
		4 00					
		10 25		100	70		
		10 40		110	70		
3	4-20	11 10	75	110	78		
		11 40		104	58		
		12 40		98	50		
		1 40					

TABLE 3

*Comparative effects of ephedrin and epinephrin in a case of chronic nervous exhaustion*

Date 1925	Time	Drug administered and amount	Blood pressure		Pulse	Remarks
			Systolic	Diastolic		
2-24	2 30	Ephedrin, 70 mg. orally	120	60		
	2 45		118	70		
	3 15		115	50	88	
	3 45		159	75	80	
	4 15		150	70	72	
	4 45		142	70	76	
	5 15		138	70	72	
	5 45					Dizziness Nausea
2-26	9 20	Epinephrin, 0.5 cc. hypodermically	105	70	92	
	9 35		118	60	96	
	9 50		118	60	88	
	10 05		110	56	96	
	10 20		106	50	96	
	10 35		105	55	96	

*Pituitary Disease.* In the first case of pituitary disease, in response to single doses of 50 mg., the effects on the blood pres-

sure were not decisive. In Case 1, Table 4, 100 mg. of ephedrin was given daily for a total dosage of 3.05 gm. (Fig. 4). There was a gradual and steady increase in the systolic and diastolic pressures. Thyroid extract was given simultaneously and the increase in blood pressure was accompanied by an increasing

TABLE 4

*Effects of ephedrin on blood pressure and basal metabolic rate*

Case	Date, 1926	Ephedrin, mg.	Time after giving of ephedrin, minutes	Basal metabolic rate	Blood pressure	
					Systolic	Diastolic
1 (Pituitary tumor)		50 (orally)	15	— 6	100	56
			30	— 11	100	58
			60	— 8	102	56
			90	— 2	108	60
				— 1	106	54
2 (Chronic exhaustion syndrome, after pregnancy)	3-30	50 (orally)	15	— 2		
			30	— 2		
			60	— 4		
			90	— 1		
				+ 5		
4- 1		50 (orally)		— 14		
			15	— 10		
			30	— 8		
			60	— 7		
			90	— 7		
4- 7	4- 7	50	9:15		98	66
			9:45		104	74
			10:15		110	72
			10:45		100	60
			11:15		100	60
			11:45		122	64
			12:15		120	76
			12:45		100	60

metabolic rate (Fig. 4). The clinical improvement in this patient was not sufficient to justify surgical intervention.

#### EFFECTS ON PULSE RATE

No significant variations were observed in the pulse rate following the administration of ephedrin alone. About an equal number showed an increase or a decrease from 10 to 15 beats a minute. In one case of Addison's disease, following a rise of systolic pressure to 176 mm. of mercury, the pulse became bounding in character and slightly irregular; the rate was 46.

## CALORIGENIC EFFECTS

The calorogenic effects of ephedrin were determined in three cases of Addison's disease, from 50 to 100 mg. of ephedrin being given orally, and the basal metabolic rate determined from

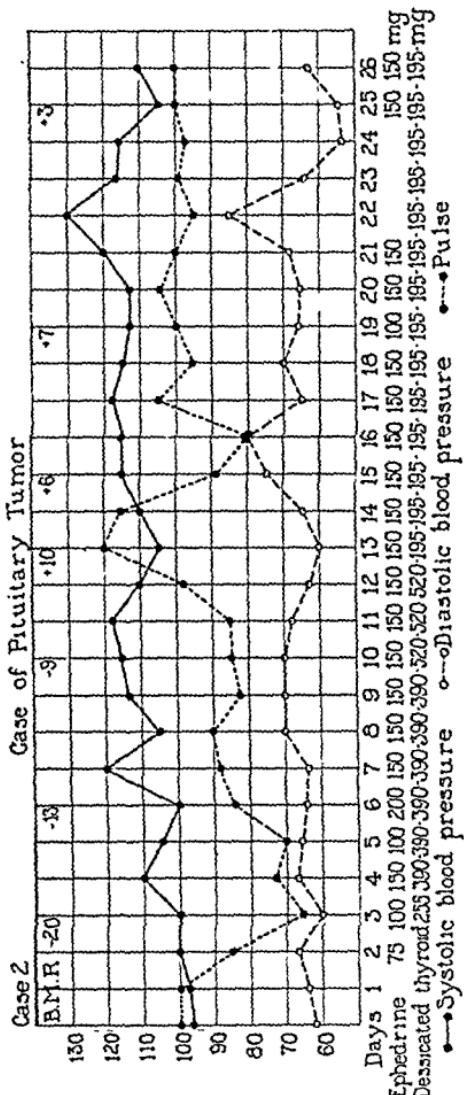


FIG. 4. A gradual increase in systolic and diastolic blood pressures after a total dosage of 3.05 gm. of ephedrin. With the simultaneous administration of thyroid extract an increase in basal metabolic rate is also noted.

four to six times at intervals of a half hour (Table 5). In Case 1 there was a drop of 12 points in the basal metabolic rate. In Case 2 there was an increase from -4 to +2. In Case 3, 100 mg. of ephedrin was given, and the basal metabolic rate increased from -27 to -17 after a period of one hour and twenty minutes.

In a case of questionable Addison's disease, the administration of 150 mg. of ephedrin was followed by an increase in the metabolic rate of from +2 to +12. This rise occurred in two hours (Case 4, Table 6).

TABLE 5

*Calorigenic effects of ephedrin in cases of Addison's disease*

Case	Ephedrin, mg.	Time after giving of ephedrin, minutes	Basal metabolic rate
1	50	30	+ 9
		60	- 3
		90	+ 3
		120	+ 4
2	50	15	- 4
		30	- 4
		60	+ 2
		90	+ 2
3	100	80	-27 -17

TABLE 6

*Calorigenic effects of ephedrin in cases with chronic exhaustion syndromes*

Case	Ephedrin, mg.	Time after giving of ephedrin, minutes	Basal metabolic rate
1 (Obesity)	50	15	+ 2
		30	- 8
		60	- 5
		90	- 7
2 (Exhaustion syndrome)	50	15	+ 1
		30	+ 4
		60	+ 2
		90	+ 7
3 (Chronic exhaustion)	50	15	- 11
		30	- 6
		60	- 13
		90	+ 4
4 (Questionable Addison's disease)	150	60	+ 2
		120	+ 9
		180	+ 12
			+ 6

The calorigenic effect of ephedrin was likewise determined in four cases of hypotension, with dosages of 50 mg. orally. A slight increase was demonstrable in all cases after a period of one hour. The effects seemed quite transitory and one hour

afterwards there was a tendency for the metabolic rate to decrease. The patient with endocrine obesity (Case 1, Table 6) showed a decrease of 11 points with 50 mg., but with 100 mg. there was an increase of 13 points in three hours. In the cases of pituitary tumor there was a demonstrable increase of the basal metabolic rate after 50 mg. of ephedrin had been given.

#### TOXIC EFFECTS

The subjective symptoms from ephedrin in doses of 50 to 100 mg. were remarkably slight. Three patients with Addison's disease manifested reactions which may have been related to the administration of ephedrin. In one case 150 mg. of the drug was administered twice daily while the full Muirhead treatment was being given. On the fourth day ephedrin was taken soon after 0.5 cc. of epinephrin had been given subcutaneously. A throbbing headache and profuse perspiration resulted, and the systolic blood pressure increased to 176 mm. The diastolic pressure was 68. The pulse was irregular and the rate dropped to 46. The reaction subsided in five minutes. No similar reactions were noted following the administration of either drug alone. It was felt, therefore, that the combination of the two drugs was probably responsible for the unusual reaction. In the second case of Addison's disease there was a slight gastric upset which may have been due in part to overexertion. The third patient complained of weakness and trembling of a transitory nature after 100 mg. of the drug had been given. Some of the patients with questionable Addison's disease manifested weakness, marked trembling, and palpitation thirty minutes after taking 150 mg. of ephedrin. The effects lasted about thirty minutes and were not accompanied by significant changes in the blood pressure or pulse rate.

The patients with hypotension seemed less tolerant to ephedrin than those with Addison's disease. Three complained of palpitation, weakness and trembling, within thirty minutes after taking the drug. In one case this persisted for four hours. These reactions were mild, and the trembling and tremor were subjective rather than objective in character. The patient with

pituitary tumor tolerated the prolonged administration of the drug remarkably well and no toxic symptoms were observed. Mild trembling was noted by practically all ambulatory patients after doses of 65 mg. or more. Patients at rest appeared to tolerate this drug better than those who were ambulant.

#### REACTIONS OF THE SKIN CAPILLARIES

Ephedrin in 10 per cent concentration in physiologic solution of common salt was used in determining the skin reaction. A drop of the solution was placed on the skin of the forearm, and several bloodless punctures were made through it with a needle. Control tests with 1:1000 epinephrin solution and with trauma alone were made. The ephedrin reaction consists of a small red central area, about 3 to 6 mm. in diameter, surrounded by a patchy white border which is quite irregular and not constant. Reflex erythema frequently appears. The epinephrin reaction consists of a small white central area surrounded by one of erythema. The trauma reaction usually consists of a small central red area with reflex erythema but no white border. The ephedrin reactions were inconstant and the capillary contractions less decisive than with epinephrin. In one case of Addison's disease the zone of constriction, or white area, was absent with ephedrin, the red center alone appearing. Further work is being carried out in this connection.

#### GENERAL CLINICAL EFFECTS

In cases of Addison's disease the results from the use of ephedrin are distinctly disappointing. We have seen no evidence of significant improvement in patients with advanced Addison's disease. Certainly the resulting moderate increase in blood pressure was not accompanied by a marked feeling of well-being, significant increase in strength, or relief from the gastric symptoms or circulatory asthenia. The subjective improvement following a Muirhead treatment is much more pronounced than that from the use of ephedrin.

Full therapeutic doses of ephedrin resulted in some subjective improvement in certain instances. An occasional patient

admitted feeling somewhat stronger for several hours following its administration. This, however, was an exception. Full therapeutic doses usually resulted in minor toxic manifestation, palpitation, and a peculiar subjective sensation of weakness and trembling.

In one case of early Addison's disease excellent clinical results were obtained, comparable in every way to those we have seen in similar cases under the Muirhead regimen. The feeling of weakness and exhaustion disappeared and the patient felt buoyant, strong and refreshed. However, the treatment was without significant effects in other early cases of Addison's disease.

In hypotensive and hyposthenic states not due to Addison's disease, ephedrin may prove of value at times. A more extensive use is advocated in this connection.

#### CONCLUSIONS

1. Ephedrin is relatively nontoxic and may be used orally, subcutaneously, or intramuscularly without undue toxic effects, in amounts sufficient to increase blood pressure and to raise the rate of metabolism.
2. While increase in blood pressure and in rate of metabolism may be demonstrated in Addison's disease as the result of ephedrin, these changes are rarely accompanied by significant subjective or objective evidences of clinical improvement.
3. Ephedrin is not an effective specific remedy in the treatment of Addison's disease. The results obtained with ephedrin have been disappointing and do not compare in value to those obtained by the Muirhead treatment.
4. Because of its low toxicity and its effect on blood pressure and on metabolism when administered orally, its further trial in other hypotensive and hyposthenic states is warranted.
5. It must not be concluded from the results reported herein that ephedrin will not prove useful in other fields; the references suggest that it will.

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# A CASE OF DIABETES INSIPIDUS ASSOCIATED WITH SYPHILIS OF THE HYPOPHYSIS \*

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Diabetes insipidus is a clinical syndrome characterized by polydipsia and polyuria. A distinction is frequently made between primary or essential, and secondary or symptomatic polyuria. In the primary variety, polydipsia and polyuria are the chief clinical symptoms; in the secondary variety, these symptoms constitute only part of the clinical picture, which is usually that of some organic brain disease. The volume of urine in diabetes insipidus varies from a slight increase above the normal to enormous quantities in twenty-four hours. The polydipsia varies with the polyuria.

Numerous clinical studies have been made of diabetes insipidus. These have brought out a number of facts but have led to a great many more speculations. Some writers have rightly termed diabetes insipidus a disease of theories. The urine in diabetes insipidus has the following characteristics: The volume is markedly increased, it is pale in color, of low specific gravity, and poor in salts as indicated by freezing-point determination. The ordinary tests of renal function have usually shown no deviations from normal, in uncomplicated cases.

Complete agreement as to the pathologic physiology of diabetes insipidus has not been reached. The idea that the kidneys lose their concentrating capacity has been generally abandoned [Meyer and Meyer-Bisch (1)]. On the basis of metabolic studies, Veil (2) maintains that diabetes insipidus is a disturbance in intermediary metabolism of water and sodium chloride. He believes that the entire organism is adjusted to a lower niveau of osmotic pressure which is the starting point of the insipidus. Meyer and Meyer-Bisch conclude that a hypotonic sodium chloride solution not only circulates through the kid-

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neys in the blood, but that the tissues yield a hypotonic solution to the blood. There seems to be a disturbance in exchange between the tissues and blood as well as between the blood and kidneys.

I have been able to collect from the literature the records of 105 cases of diabetes insipidus with autopsy findings. The pathologic lesions held responsible divide themselves into three distinct types, depending upon the prevailing theories and experimental production of polyuria. The first period was influenced by Claude Bernard's classical experiments (3) in which he demonstrated that pique of the floor of the fourth ventricle led to polyuria, and lasted until 1912 when Frank (4) directed attention to the frequent association of diabetes insipidus with signs of hypophysial lesion. The second period may be termed the hypophysial period and extends from 1912 to 1920. During this period special attention was directed toward the hypophysis, other lesions being accorded secondary importance, and when gross lesions were absent, it was maintained that pressure upon the hypophysis by distant lesions might cause polyuria. The third period is again based upon experimental physiology and finds its origin in the work of Camus and Roussy (5), who showed that injury to the floor of the third ventricle near the insertion of the infundibulum leads to polyuria. There is a distinct tendency at the present time to minimize the importance of lesions of the hypophysis and revert to the cerebral idea of the etiology of polyuria.

Leschke (6) was among the first to maintain that diabetes insipidus is due to a lesion at the base of the midbrain, and based his arguments upon a large amount of clinical and experimental material. He gives protocols of 16 cases in which there was complete destruction of the hypophysis without polyuria. A careful study of such cases was made by v. Hann (7), who compared them with cases of diabetes insipidus in which pathology of the hypophysis was found. He concludes that the occurrence of polyuria depends not only upon the condition of the posterior lobe, but on that of the anterior lobe as well. Disturbances of the posterior lobe with an intact anterior lobe lead to diabetes insipidus; if the anterior lobe is injured at the same time as the posterior lobe, diabetes insipidus does not develop. Extension of the process to the anterior lobe may cause

an existing diabetes insipidus to disappear. This would account for such cases as Simmonds (8) reports in which a metastasis from a carcinoma of the breast produced polyuria which later disappeared.

That lesions of the base of the midbrain do not invariably produce polyuria is abundantly proved by reports of cases, usually tumors of the hypophysial anlage, which involve this region not associated with polyuria.

#### REPORT OF CASE

The patient, an Austrian garment worker, was admitted to the Cook County Hospital, on the service of Dr. Jos. Miller, August 17, 1915, and discharged on August 24, 1915. He was then 40 years old. His complaints were: incontinence of urine, weakness, polyuria, impotence, constipation and a constant feeling of chilliness.

*Onset and course.* The onset was about eight years before (in 1906) with an attack of headache and vomiting. The headache was very severe and constant, lasting about a month. Two months later he developed great thirst and entered a hospital in Toronto. He stated that he drank 10 to 12 gallons of water a day and passed 360 to 400 ounces of urine. After receiving medical treatment for about six months, he came to Chicago to work as a tailor. Since then he has been drinking much water and passing large quantities of urine. Up to April, 1915, he felt fairly well and then began to have nocturnal incontinence. One month before admission (July, 1915) he noticed increased fatigue and sensations of extreme heat on the soles of his feet and over the buttocks. The same day he passed about a quart of blood while attempting to urinate. He has been extremely weak since then. Sexual desire has been absent for eight years.

*Past History.* Until the onset of the present complaint he had been in good health. He passed through an attack of smallpox when three years old which was complicated by an infection in the right eye and loss of vision in that eye. He had a chancre in 1901 and gonorrhoea three or four times.

*Family History.* He has one child, eleven years old, living and well. His wife is divorced.

*Physical Examination.* The patient was very anemic and appeared to be in a weakened condition. The right cornea was opaque and there was no vision in that eye. The teeth were carious and the mucous membranes pale. A few subcrepitant rales were found in the right side of the chest. There was almost total absence of pubic hairs and the testes were small and atrophic. The prostate gland was tender; the epididymis appeared to be normal. An attempted cystoscopic examination was unsuccessful because the urethra was too small to admit a catheter. Examination in the eye depart-

ment on August 27, 1915, showed normal vision in the left eye and total blindness in the right eye due to phthisis bulbi. The visual field showed no scotomata or hemianopia. The fundus was normal.

*Laboratory Findings.* Examination on August 24, 1915, gave the following data: Urine volume, 2,000 c.c.; specific gravity, 1.012; reaction alkaline, no albumin, no sugar; spinal fluid Wassermann, negative; hemoglobin, 70%; red blood cells, 3,040,000; color index, 0.9 plus; white blood cells, 10,500; differential count, 54% polymorphonuclear, 40% small mononuclear, 5% large mononuclear, 1% eosinophile.

A radiogram of the skull on August 19, 1915, disclosed a definitely abnormal outline of the sella. The posterior bony portions, including the posterior clinoid processes, were absorbed, indicating pressure by an enlarged pituitary gland.

The diagnosis made by Dr. Joseph L. Miller was diabetes insipidus, hypophyseal dystrophy and cerebral lues. The treatment consisted of mercury rubs, iodides by mouth and hypodermic injections of pituitrin three times daily. A sugar tolerance test was made by Dr. Russell Wilder, November 13, 1915, using intravenous injections of various strengths of sugar solutions by the Woodyatt method; this showed tolerance at the lower limit of normal, or 0.8 gm. per kilogram body weight per hour.

The patient was discharged at his own request on December 28, 1915, somewhat improved.

He was readmitted on June 19, 1916. His chief complaint at this time was inability to control his urine. Examination showed him to be well nourished, not acutely ill, or in discomfort. The skin was white and smooth over the entire body. There was a noticeable lack of hair over the chest and a scanty supply on the chin and face, and almost complete absence of hair on the shins and arms. The skin, mucous membranes and tongue were extremely dry. The systolic blood pressure was 135, diastolic 90, pulse pressure 45. The blood and spinal fluid Wassermann tests were negative. June 30, 1916, the average daily volume of urine was 3,000 to 3,500 c.c., and dropped to 2,000 to 1,800 c.c. with intramuscular injections of pituitrin. A renal function test yielded the following result: phenolsulphonphthalein first appeared in 25 minutes; 5% in the first hour and 10% in the second hour, making a total of 15% elimination of the dye in the first two hours.

The patient left the hospital July 21, 1916, and returned for the third time December 2, 1924. He was then 50 years old. In addition to previous symptoms there was nausea and severe vomiting and he had become so weak that he was unable to work.

Physical examination showed him to be very pale and poorly nourished. His blood pressure was up to 164 systolic and 98 diastolic, pulse pressure 69. The reflexes were exaggerated, there was

a bilateral positive Babinski sign and ankle clonus. The skin was lemon yellow in color, dry and harsh.

*Laboratory Findings.* The hemoglobin proved to be 60% of normal; red blood cells, 2,800,000; leucocytes, 9,800; polymorphonuclears, 58%; lymphocytes, 36%; large mononuclears, 6%. Urinary excretion ranged between 2,500 and 3,000 c.c.

A roentgenogram of the skull on December 5, 1924, showed the sella to be shallow in proportion to the antero-posterior diameter, being deeper in the dorsal than the anterior half; the floor was well defined.

The patient was discharged January 19, 1925, and returned for the last time March 21, 1925. He was then so weak he could not walk, had lost 30 pounds in a few months and frequently vomited a greenish material unrelated to food taking. Polydipsia and polyuria had disappeared for the past few months. Frontal headache had been present for a few days, but no convulsions.

Physical examination revealed a white male about 56 years old, poorly nourished, with a lemon yellow tint to the skin and apparently acutely ill. His pulse was of very poor quality and thready. He was mentally sluggish. Blood examinations showed hemoglobin, 65%; red blood cells, 3,230,000; white cells, 24,200; polymorphonuclears, 85%; lymphocytes, 15%; no abnormal red cells were noted. The urine was reduced to 450 c.c., with specific gravity, 1,008; no albumin and no sugar. The temperature was normal or subnormal throughout. He continued to vomit excessively, being unable to retain anything by mouth, and died April 1, 1925.

#### SUMMARY OF THE CLINICAL HISTORY

The history is that of diabetes insipidus of about 20 years' duration, the onset occurring about 5 years after a primary lesion, with symptoms suggestive of syphilitic meningitis. At first the polydipsia was extreme and the polyuria enormous. Both improved temporarily under anti-luetic treatment and were partially controlled by hypodermic injections of pituitrin. Signs of hypophyseal dystrophy developed, consisting of loss of body hair, moderate adiposity and atrophy of the genitals, constituting the adult type of Froelich's syndrome or dystrophia adiposo-genitalis. During the last few months before death his diabetes insipidus had apparently disappeared.

#### AUTOPSY FINDINGS

The autopsy was performed by Dr. H. Gideon Wells on the day of death.

*External Appearance.* The body was that of a slender, poorly nourished but not emaciated man, appearing much younger than his

age. The hair of the head was abundant, dark, and with a few gray hairs. Eyebrows were present, but not heavy. The skin was pale. There was some blood crust on the lips and gums, and the mucous membranes were pale. The teeth were in bad condition. The sclerae appeared normal, but the right cornea was opaque. The superficial lymph nodes were not enlarged. There was a marked sparseness of body hair—none at all in the axilla, five or six in the pubic region, and about as many on the chin; none on the scrotum, thighs, arms, or elsewhere on the face or body. The testicles were small and soft. The penis was normal. There was a suggestion of superficial atrophic scars on the body of the penis. There was a slight palpable edema of both lower extremities and of the right wrist. There was distinct hypostatic edema. On opening the body, an abundance of subcutaneous fat of a lemon-yellow color, about 1 cm. in thickness, was exposed along the mid-line, not only over the abdomen, but also over the chest, and much more than would be expected from the slenderness of the body, that is, the subcutaneous fat resembled in distribution that of the female rather than the male, and there was a distinct thickening of the fat above the pubis to form a definite mons veneris.

*Mouth and Pharynx.* The tongue showed atrophy of the dorsal surface. The central part was covered with blood-stained crusts. The tonsils were atrophic, but contained pockets with a cheesy content. The lymphoid apparatus at the base of the tongue was distinctly atrophic.

*Thyroid and Thymus.* The thyroid gland weighed about 10 gms. The parathyroid glands could not be definitely located. The thymic body was replaced by fatty adipose tissue.

*Heart, Aorta and Vessels.* The heart appeared about normal. There were yellow patches in the aorta, especially in the arch. The aorta was of about normal size and still elastic. It showed distinct areas of thickening and wrinkling at the orifices of the subclavian and innominate arteries. There was a depressed calcified area, 10x15 mm. in the arch. The orifices of the coronary artery were of normal size, but there was a definite sclerotic patch in the anterior coronary artery just beyond the orifice. The posterior coronary artery also showed patches of sclerosis.

*Liver.* The external surface of the liver showed numerous depressed scars. It weighed 960 gms. and was brown in color. The surface scars ran into the substance of the organ, from 5 to 15 mm. Cut surface showed no further scarring or other changes.

The pancreas was small and weighed 50 gms. It showed no gross abnormalities.

*Adrenals.* The left adrenal was very small and atrophic. The right resembled the left. The cortex was reduced to a mere line of yellow, the medulla showing less reduction, but all told each adrenal was scarcely a millimeter thick, and about half the usual length and

breadth. They showed central postmortem softening and were so much involved in the perirenal fibrosis that they could not be successfully isolated for weighing.

*Kidneys.* The kidneys were excessively adherent to the perirenal fat. The left kidney was partly converted into a sac by distension of the pelvis. The cortex was thin, 1-2 mm., and the pyramids were about 5 mm. wide. The capsule was adherent, but when torn showed a very granular surface. The right kidney resembled the left. No evidence of acute inflammation was noted.

*Urinary Tract.* The urinary bladder and ureters were greatly distended. The bladder reached to the pubis and showed marked hypertrophy of the wall, but the mucosa was not inflamed. The ureters were about 10-15 mm. in diameter, but not inflamed.

*Generative Organs.* The testicles were about equal in size and measured each about 10x15 mm. They consisted of pale homogeneous tissue with no visible glandular elements. The prostate was atrophied to such a degree that it was not readily discerned. The seminal vesicles were empty and atrophied to thin fibrous cords with brown centers. The urethra showed a small amount of scarring at the junction of the prostatic and penile portions, but was not completely occluded.

*Brain and Meninges.* The calvarium was thin and weighed 350 gms. It was symmetrical and showed nothing abnormal. It did not adhere unduly to the dura. The dura was thick and opaque. The amount of cerebrospinal fluid was rather large, but not greatly excessive. The optic chiasma was free, but there were adhesions in the pia about the infundibulum and floor of the skull, which adhesions seemed limited to this area. The brain as a whole showed a slight degree of atrophy of the convolutions, i. e., the sulci were increased in prominence. The brain weighed 1,440 gms. The pia and arachnoid showed no thickening indicative of a syphilitic leptomeningitis. The arteries at the base of the brain were not apparently thickened. The sella turcica was shallow and flat. The hypophysis was extremely small and reduced to a flat disc 11 mm. transversely, 7 mm. vertically, and 1-2 mm. thick, including the thickened capsule which was not to be differentiated from the thickened dura, with which it merged. There was no distinct hypophysis and its location was determined solely by the entrance of the infundibulum into the thickened fibrous tissue.

#### MICROSCOPIC EXAMINATION

The hypophysis, including the adherent dura and blood vessels, was imbedded in celloidin and the entire mass completely sectioned. The infundibulum, posterior lobe and pars intermedia were replaced by dense avascular scar tissue. No remains of the anterior lobe were found until the middle of the block, where there appeared a mass of glandular tissue measuring about 2 mm. in diameter. This

again gradually faded out into fibrous tissue. The cords of epithelial cells were compressed and the sinusoids dilated and filled with blood, giving the impression of passive congestion. A number of sections contain the carotid artery lying just outside the anterior lobe. This shows a moderate endarteritis and a small area of calcification in the media.

The base of the brain was divided into four blocks, imbedded in paraffin and cut in serial sections. These were stained with hematoxylin and eosin, van Giesen and Mallory's connective tissue stains. The collections of ganglion cells scattered through the hypothalamic region and in the tuber cinereum appeared well preserved. The ependyma lining the third ventricle was intact. Nowhere was there any perivascular round cell infiltration. Some of the small blood vessels were slightly thickened, but no distinct endarteritis was present. Dr. Hassin examined these sections and stated that, in his opinion, the normal architecture of this portion of the brain was intact.

*Kidneys.* The capsule is thickened and adherent to the surface of the kidney where there is a layer of round celled infiltration replacing the outer part of the cortex and running along fibrous areas into the pyramids. There is a similar round cell area and a heavy fibrous layer beneath the epithelial surface of the pelvis. There remains but a small amount of renal tissue in which the tubules are dilated and filled with protein. The vessels show marked arteriosclerosis. No acute suppurative changes are present.

*Testicles.* The glandular elements are almost completely replaced by fibrous tissue. Remains of the tubules are seen, but none contain distinct epithelial structures.

The seminal vesicle is distinctly atrophic and collapsed.

*Prostate.* This consists of fibro-muscular tissue with a larger proportion of fibrous than muscular elements. There are a few collections of small collapsed tubules staining almost black with hematoxylin as if partially calcified.

*Adrenals.* The cortex is extremely thin, the cells small and poor in lipoid. The medulla is abundant, and seems normal.

*Thyroid.* The acini are extremely small, although most of them contain colloid. The arteries are calcified. No other changes are seen.

*Thymus.* The thymus shows numerous areas of lymphoid tissue scattered through the fat, slightly more than is usual at this age.

*Pancreas.* Seems entirely normal.

*Liver.* There are scars beneath the capsule. The lobules and cells are small, but no diffuse fibrosis or other changes were noted.

*Aorta.* The aorta was much thickened with atheroma in the intima and occasional old scars cutting across the media, but there are no active syphilitic changes.

*Tongue.* A section near the base shows an absence of lymphoid tissue, which is replaced by fibrous tissue.

*Anatomic Diagnosis:* Bilateral hydro-uretero nephrosis with chronic interstitial nephritis; hypertrophy and dilatation of the urinary bladder; syphilitic aortitis; slight aortic endocarditis; syphilitic scars of the liver; marked atrophy of the testicles, prostate, seminal vesicles, adrenals, thyroid and hypophysis; feminine distribution of body fat; nearly complete absence of body and facial hair; meningeal adhesions about the infundibulum; bilateral adhesive fibrous pleuritis; multiple healed nodular tuberculosis of both lungs; fibrous prostatitis; diffuse suppurative bronchitis and tracheitis; left suppurative otitis media and mastoiditis; atrophic glossitis; slight hypostatic subcutaneous edema; opacity of the right cornea; slight general atrophy of the viscera; atrophic pulmonary emphysema; slight brown atrophy of the heart and liver; incomplete stricture of the urethra.

#### SUMMARY OF THE PATHOLOGIC FINDINGS

How do the pathologic findings account for the clinical picture? The diabetes insipidus must be attributed to destruction of the posterior lobe of the hypophysis. The tuber cinereum and the entire base of the brain were normal in architecture and no grossly recognizable lesion was found in sections stained by the ordinary methods in use. The polyuria disappeared because of renal insufficiency, the terminal symptoms being those of uremia, resulting from stricture of the urethra, repeated ascending urinary infections and chronic interstitial nephritis. The ultimate cause of death was a complication of gonorrhoea, and his first illness was due to syphilitic basal meningitis with possibly a gumma in the posterior lobe of the hypophysis.

The polyglandular syndrome is not easily explained. The same difference of opinion exists regarding the basic pathology of Froehlich's syndrome as is the case with diabetes insipidus. I am inclined to believe that there was enough reduction in anterior lobe substance to produce functional insufficiency. On the other hand, syphilis may have produced diffuse atrophy of the testes, and the changes in the other endocrine glands occurred secondary to this. Yet diffuse atrophy of the testes is common in syphilis of long standing, and it is usually not accompanied by changes in other glands of internal secretion.

A number of points should be emphasized. First, that in our conception of the pathology of diabetes insipidus we cannot ignore those cases in which the lesion is confined to the posterior lobe and infundibulum of the hypophysis, nor the fact that when polyuria develops in a case of malignancy, it is

almost a pathognomonic sign of the presence of a metastasis in the posterior lobe of the hypophysis. Second, that the hypophysis and midbrain are anatomically united and in view of our present knowledge we must consider the hypophysis and the centers in the midbrain as a functionally united system. The rhythmic automaticity of the respiratory centers is dependent upon the chemical composition of the blood, and we may logically assume that the regulatory activity of the vegetative centers in the midbrain is influenced by the internal secretory function of the hypophysis. This is the view recently expressed by Berblinger (9), and is consistent both with the facts obtained from a study of pathologic anatomy, including circumscribed lesions of the hypophysis that cannot be duplicated artificially, and the evidence of experimental physiology and anatomy. The purely nervous theory of the genesis of polyuria no more solves the problem of diabetes insipidus today than did Claude Bernard's demonstration of pique centers in the floor of the fourth ventricle solve the problems of both diabetes insipidus and diabetes mellitus.

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# THE THERAPEUTIC INDICATION FOR THE USE OF ANTERIOR PITUITARY LOBE SUBSTANCE.\*

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The practice of organotherapy is not a modern idea. It dates back many centuries when medicine was shrouded with mysticism and superstition. Progress was necessarily slow, as it had to advance along empirical lines. Although Hippocrates, Celsus and Dioscorides employed certain animal tissues in the treatment of diseases and the four London Pharmacopeias of 1618, 1650, 1677 and 1721 abounded with such remedies as blood, bile, bones, brains, excrement, fat, hearts, marrow, urine, etc., they finally fell into disrepute largely through Thomas Sydenham, who did not attach much importance to them, and later through William Heberden, who made a critical onslaught on polypharmacy and banished these remedies from the British Pharmacopeia in 1788. From this period until quite recently, when the modern sciences were beginning to be applied to medicine, little effort was made to re-introduce them. However, owing to a more comprehensive knowledge of the anatomy, histology and physiology of the glands of internal secretions and the various symptomatic manifestations produced through the arrest or alteration of their secreting function by modern scientific methods of experimental research on animals, definite clinical, pathological and anatomical bases were established for organotherapy. It is surprising to note the rapidity with which the indications have been met and how closely therapeutics followed the wake of physiological investigation. This has been particularly true of the thyroid, which served as the entrance wedge into the domain of endocrinology. Advancement in the study of the hypophysis was relatively slow because of the inaccessibility of the gland. It was not until 1906, when Paulesco developed a special surgical technique that a portion of the gland could be extirpated without death resulting to the animal. As a consequence of innumerable subsequent experiments the function of the hypophysis is now pretty well understood. Briefly these experimental results may be summarized as follows:

\*Paper presented at the annual meeting of the American Therapeutic Society held in Philadelphia, June, 1926.

A. The removal of the whole gland is uniformly fatal, producing tremor, muscular fibrillation, low temperature, slow pulse and respiratory rate, stupor and coma.

B. Removal of the posterior lobe does not cause death, although a deficiency causes hypotension, increased sugar tolerance, decreased basal metabolism and asthenia.

C. Complete removal of the anterior lobe causes a cachexia which terminates in death.

D. Partial removal of the anterior lobe causes obesity, genital hypoplasia, faulty skeletal development and hypothermia; the latter can be prevented by injection of an extract of the anterior lobe. In as much as organotherapy can only be rationally applied to deficiency glandular syndromes, the effects produced by overfunctioning of the pituitary gland need not be considered here.

Reasoning on the basis of cause and effect, it would appear that the administration of anterior pituitary lobe extract should yield favorable results in conditions arising from insufficiency of the lobe, namely, retarded skeletal growth, pituitary obesity, delayed puberty, genital hypoplasia, and hypophyseal cachexia.

Unfortunately the pharmacology of the anterior lobe is still meager as compared with that of the posterior lobe. In 1916 Robertson obtained a soluble lipoid, which represented some of the active principles of the anterior lobe and exerted a control over growth; to this substance he applied the name tethelin. Various feeding experiments of anterior lobe on animals and tadpoles by numerous investigators led to a division of opinion as to its pharmacodynamic effects. These discrepancies were apparently due to the age, species and growth period of the animals, the amount of gland feeding and the duration. The final analysis, which conclusively showed that anterior lobe administered orally has a distinct therapeutic effect in deficiency syndromes, depended upon the results obtained by the extensive use of this substance in the human being, so that its action is no longer a mooted question. The important desideratum is the correctness of the diagnosis in order to ascertain the proper indication for its use.

My personal interest in anterior pituitary therapy was incited by the study and observation of a patient who came under my care in 1915. This case, in addition to a group treated subsequently, was reported under the caption of "Fat Redistribution in Dystrophia Adiposogenitalis," in the Journal of American Medical Sciences, November, 1918, p. 714. The case referred to was a woman aged 41, married and weighing 125 pounds. She was a confirmed invalid by reason of three fairly well defined groups of signs and symptoms, namely: those referable to pituitary insufficiency; girdle adiposity and genital hypoplasia; those referable to gonadal insufficiency: frigidity, sterility and amenorrhoea, and those referable to thyroid insufficiency: apathy, stupor, dullness and neuromuscular and trophic skin disturbances. The outstanding feature was her obesity, although she had gained about twenty pounds in the previous ten months the only noticeable increase was confined to her hips, thighs, gluteals and lower abdomen.

Regarding her symptoms of pluriglandular origin in which the thyroid, pituitary and ovaries were involved, the three respective hormones were administered with singularly marvelous results. Her general condition rapidly improved so that she was able to resume her housework, but more striking was the change in her body configuration. Measurements obtained from her dressmaker, taken two weeks before treatment was begun and eleven weeks afterwards, showed a reduction in the size of her hips seven and a half inches and of the waist five inches. She had lost only one pound in weight. The face, neck, chest and arms, which before treatment presented the appearance of emaciation, had filled out and the configuration of the body returned to normal. Treatment was discontinued after five months and there has been no return of her symptoms.

This case afforded convincing proof that the therapeutic results in the girdle type of dystrophia adiposogenitalis cannot be gauged by the effect of glandular treatment upon the weight of the patient, and established the fact that a better criterion is a record of systematic circumference measurements which have been adopted. These measurements are the maximum hip, minimum waist, axillary, neck, thighs at the groin, knees and ankles. In the "System of Endocrinology and Metabolism," published

in 1922, the writer reported forty-six cases of pituitary fat dystrophy studied and treated in this manner. These patients usually received thyroid in doses of one to two grains a day and anterior pituitary lobe in doses of five to ten grains a day, although in some of the cases good results were obtained with anterior pituitary lobe alone.

The reason for administering thyroid in conjunction with anterior pituitary lobe is on account of its influence in accelerating general metabolism and its stimulating effect upon the pituitary and sex glands. Moreover, the thyroid gland is so closely related functionally with the pituitary that it is frequently a concomitant etiological factor. In this class of cases it has a dual action, namely: supplying the lack of thyroid hormone in an associated thyroid deficiency and stimulating the function of the anterior lobe of the pituitary. The tabulated results of the forty-six cases reported showed definitely marked improvement in twenty-six cases, in sixteen of which there occurred typical fat re-distribution as indicated by an increase of the circumference measurements above the waist and a decrease below the waist in addition to the general improvement of the patient. Nine cases showed moderate improvement, but without typical re-distribution of fat. Eleven cases remained unimproved. In most of these cases the treatment was not administered a sufficient length of time to derive any real benefit. Since the report of this series the number of cases treated has almost doubled with practically the same results.

In the Fröhlich type of dystrophia adiposogenitalis (or the pre-adolescent form) advice is often sought in regard to some of the cardinal features of the disease, such as stunted growth, sexual infantilism, delayed puberty, amenorrhoea, etc. If these conditions are caused primarily by reason of insufficient anterior pituitary secretion good results are obtained by pituitary feeding either by itself or in combination with thyroid.

In pituitary dwarfism in which skeletal growth was arrested at an earlier age than normal puberty and the epiphyses are still ununited, anterior pituitary feeding will frequently cause a renewal of skeletal growth even after cessation for a number of years. The following case is cited as an example: W. F., male, aged seventeen years and one month, weighed  $51\frac{1}{2}$  pounds and

measured 130 cm. in height, which, according to normal standards of height and body weight, represents the average boy eight years of age. He was normal at birth and developed normally, both mentally and physically, until this age, when he ceased to grow, although he continued to develop mentally. Besides cessation of growth he exhibited certain features characteristic of hypopituitarism, namely: maxillary prognathism; absence of beard, hirsutism and crines pubes; soft, delicate skin; infantile voice; genital hypoplasia; delayed epiphyseal union and sellar deformity. Treatment was begun in October, 1921. In this case whole pituitary gland was administered in doses varying from two to six grains a day, with the hope of benefiting the asthma from which he was suffering as well as to promote skeletal and genital growth. In December he measured 131½ em., February, 1922, 132¾ em., and September, 1922, 137 cm., which represented a gain of 7 cm., or almost three inches, in less than a year. Besides, he gained twelve pounds in weight. He was relieved of asthma and felt perfectly well. No thyroid was administered.

In other cases the same effect upon growth was produced by feeding anterior lobe alone. The reason for citing this case is to demonstrate the fact that certain cases of asthma associated with disturbed function of the pituitary apparently yield to pituitary therapy which is attributed to the effect of the posterior lobe. Unquestionably the stimulating effect upon growth is due to the anterior lobe extract. Crofton (An Outline on Endocrinology) reports a boy aged seventeen years who grew five inches in less than a year on two grain doses of anterior pituitary lobe. McGraw observed that in cretinoid dwarfs, growth is much accelerated by administering anterior pituitary lobe extract in addition to thyroid.

*Delayed puberty:* By the experimental feeding of rats with anterior pituitary lobe, some observers have shown that the animals matured sexually much earlier than their controls—according to Goetsch, in one-third of the normal time. Posterior lobe extract produces no such effect, in fact it exerts an inhibiting influence upon growth. The stimulating effect of anterior pituitary lobe upon growth applies to both the genital system and to growth in general. One can thus appreciate the rationale of

administering anterior pituitary lobe in delayed puberty and sexual infantilism in early life and distorted sexual functions such as loss of libido and potentia in adult males and amenorrhoea, frigidity and sterility in adult females, especially when these conditions are associated with other signs and symptoms of hypopituitarism. Splendid results have been obtained in boys in whom the secondary sex characteristics failed to appear at the age of puberty and likewise good results have frequently been obtained in girls who did not menstruate at the age of fifteen or sixteen. In this group of cases the treatment is more efficacious if small doses of thyroid are added.

The following case illustrates the effect of organotherapy upon amenorrhoea in a woman with adult hypopituitarism. She was twenty-eight years old and married, but had no children. Following an attack of influenza she developed a state of hypopituitarism. Her weight increased from 158 pounds to 228 pounds in four years. At examination she presented the following features: marked girdle adiposity, soft delicate skin, macroglossia, hypotension, increased sugar tolerance, monomucleosis, abnormally large open sella, bitemporal headaches, amenorrhoea and sterility. A diagnosis of hypoplasia of the reproductive organs was made by Dr. Richardson. Menstruation ceased in September, 1922, and had not returned at the time of examination. July 21, 1923. At her last consultation, January 28, 1924, records show that she menstruated in October, December and January. She had lost fifty-one pounds and her body configuration was almost normal. The headaches had disappeared and, according to her own statement, her strength and endurance had increased 100 per cent. The treatment consisted of two grains thyroid and five to ten grains anterior pituitary lobe daily.

The epileptic episodes which occasionally accompany pituitary disorders are sometimes favorably influenced by organotherapy. Cushing reported several cases in which pituitary feeding ameliorated the attacks, and Beverly Tucker reported a series of cases in which it was of marked benefit. Other observers have reported cases apparently cured by this treatment. Pituitary was administered either in the form of whole gland or anterior lobe extract. The favorable results obtained in a

patient under my personal supervision have been attributed to organotherapy. The patient referred to me by Dr. Maxson was a boy aged 13 years with a negative family history. He was normal at birth and his physical development was normal as a child. At an early age he manifested a nervous trend. He was restless and emotional and cried almost daily. At six he entered school. He was mentally delinquent and unable to keep up with his studies and make his grades in school. At eleven years of age he had an attack of influenza, which was followed by epileptic seizures. The severe attacks were characterized by sudden onset with fall, loss of consciousness and tonic and clonic spasms. In the milder forms the loss of consciousness was not complete and the spasmodic contractions were slight. The seizures increased in frequency, occurring almost daily; sometimes he had as many as four or five in one day. On May the tenth, 1920, treatment was begun with anterior pituitary lobe and small doses of thyroid. The seizures promptly ceased. On July 26th, 1920, his pastor made the following statement in a letter,—“he is doing fine. He has not yet suffered any check in progress and bids fair to become a real boy, just as surely as he bade fair to become an imbecile.” The fact is that he became mentally alert, pursued his studies and passed his grades creditably through high school. He has not had any attacks now for a period of six years and at present is actively engaged as a mechanic in a garage where he measures up to the standard of a normal healthy individual. In this case the mental processes were undoubtedly accelerated by treatment and the delinquency, which was an important factor, was completely overcome. Other instances have occurred in my practice in which marked improvement was noted in this regard. Only two weeks ago a girl with pituitary obesity and mental sluggishness, which retarded her progress in school, volunteered the information that she is doing much better in her class work and that her examination marks in two branches were one hundred. This improvement occurred while she was taking anterior pituitary lobe. It is doubtful whether it is of any value in psychiatric practice, although some psychiatrists state that improvement followed its administration in certain forms of psychoses.

*General consideration:* From the clinical results obtained by the oral administration of anterior pituitary lobe in carefully

selected cases over a period of ten years the writer is convinced of its merits as a therapeutic agent. During the same time he has learned to recognize its limitations. After all, the indications are few and can be established only by a complete and thorough study of the patient in reference to pituitary function as well as the function of other endocrine glands which may be simultaneously affected. The hormopoetic system with its chain of glands is analogous to the hemopoietic system which comprises the circulating blood, spleen, bone marrow, lymphatic glands, etc.; any one, two or more of these organs may be concerned etiologically in diseases of the blood, the picture being dominated by the organs involved. The same is true in diseases of the ductless glands, which may be uniglandular but are more frequently of pluriglandular origin. The relative importance of the respective glands involved must be evaluated by a careful analysis of the history and clinical manifestations before considering glandular therapy. Whether one is justified in feeding mixed gland depends upon such an analysis. Failure in obtaining satisfactory results are often due to injudicious combinations or over-doses.

In order to obtain the best result with anterior pituitary lobe it is necessary that the gland preparations be fresh, the dose adequate but not excessive and the duration of treatment extended over a sufficient period of time—rarely less than six months, frequently a year or more. In a large number of cases treated, no advantage was seen in giving large doses from fifteen to thirty grains a day over smaller doses of from five to ten grains a day. On account of the protracted period of treatment, additional expense and discomfort to the patient, the hypodermic method was found impractical. Moreover, there was a greater tendency for patients to abandon treatment long before the desired results were achieved than in those to whom treatment was given orally.

Whenever thyroid was administered in addition to anterior pituitary lobe its tolerance was first established by beginning with small doses, one-quarter of a grain to one-half of a grain twice a day and increasing gradually over a period of two weeks before anterior pituitary lobe was added. The maximum dose of thyroid was rarely over two or three grains daily.

# Abstract Department

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## Intracardiac injection of epinephrine in apparent death of new-born.

Garipuy & Mériel (P.), Presse méd. (Par.), 1926, 34, 180-181;  
Abst., J. Am. M. Ass., 86, 1227.

Reanimation of the heart by intracardiac injection of epinephrine is being more and more frequently reported by reason of the simplicity of the technic. Especially in syncope resulting from chloroform, the method has proved good. It was logical, therefore, to employ it in other cases of arrested heart beat. Garipuy and Mériel of Toulouse report a favorable result from intracardiac injection of epinephrine in a case of asphyxia in the new-born. In their case of an infant born apparently dead, without heart beats or pulsation of the umbilical cord, aspiration of mucus and artificial respirations had proved ineffectual. After five minutes an intracardiac injection of 1 cc. of a 1:1,000 solution of epinephrine was administered in the fifth left intercostal space midway between the median and mammillary lines. Almost immediately the infant heaved a sigh and the heart began to beat. Artificial respiration was continued, and at the end of fifteen minutes normal respiration was established. The authors pointed out that, in infants, intracardiac injection is exceedingly simple. The lungs of the infant that has not yet breathed lie flat against the vertebral column. There is, therefore, no danger of injuring them in making a puncture between the median and the mammillary lines. After the lapse of from ten to fifteen minutes, all hope of resuscitation will be gone. Therefore, no time should be lost, and, when ordinary maneuvers have failed, intracardiac injection of epinephrine should be given without delay. It will have every chance of being effectual if it is done within five or six minutes after the arrest of the heart beat. After the injection, artificial respiration and rhythmic traction of the tongue should be kept up. The injection of epinephrine is not supposed to supplant, only to supplement, these methods.

## Epinephrine injections in relapsing fever and malaria. Mishtchenko

(I.), Prophylaktitcheskaia Medizyna (Kharkoff), 1926, 5, 20-24;  
Abst., J. Am. M. Ass., 86, 1408.

Mishtchenko recalls Zlatogoroff's epinephrine test in relapsing fever. A dose of 0.5 cc. of 1:1,000 epinephrine solution is injected subcutaneously in patients with relapsing fever, and the temperature is taken every two hours. If the temperature does not rise, the

injection is repeated 48 hours later. If the temperature continues within normal range after the second injection, this is accepted as a negative reaction. With a positive reaction, fever occurs within twelve hours after the injection. Personal experience has confirmed that relapses need not be feared as long as the epinephrine test is negative. The positive test was most pronounced between the fourth and seventh days following an attack. Contraction of the spleen and consequent expelling of specific spirochetes into the general circulation may explain the positive response to the epinephrine. The test was always negative in cases of reinfection. The epinephrine test was valuable also in diagnosis of malaria treated recently or insufficiently. The mechanism was the same, the expelling of plasmodia into the blood. The injection seemed harmless.

**Adrenal and nervous factors in blood pressure (Intervention des réactions adrénalino-sécrétoires neuro-vasculaires dans la correction des troubles de la pression artérielle chez le chien).** Tournaire & Chabrol, Société de Biologie, 1926 (April 24); Abst., Paris M. J., 16, 475.

The authors have shown that the lowered pressure resulting from the loss of a large amount of blood from the carotid artery in the dog provokes simultaneously: (1) a discharge of adrenalin as shown by the method of anastomosing the adrenal vein of one animal to the jugular of another; (2) a vasoconstriction of the kidney, resulting in change of volume of this organ, previously lowered by an irrigation of blood at constant pressure. This is done by direct perfusion, through anastomosis of the arterial circulation of a normal dog with the renal artery of the experimental dog.

—R. G. H.

**Adrenals and oestrous cycle (Surrenale et cycle sexual).** Watrin (J.), Rev. franç. d'Endocrinol. (Par.), 1926, 4, 45.

The author proposed to verify with guinea pigs the experiments which Riddle made with pigeons. He injected young immature guinea pigs with varying doses of from 2 to 4 cc. of the follicular fluid obtained from puncture of Graafian follicles that had reached maturity. The modifications noted were intense congestion of the vagina, uterus and tubes. With respect to the adrenals, however, he observed nothing except a slight congestion of the cortical substance. He concludes that the follicular phase of the oestrous cycle does not influence the adrenal glands, at least in guinea pigs, and he believes this is also true in rabbits because he has never observed any reaction in the adrenals of rabbits when the Graafian follicles were mature.—R. G. H.

New clinical aspects of the Steinach operation. Benjamin (H.), M. J. & Record (N. Y.), 1925. Reprint pp. 1-39.

The author reports upon his results with the Steinach operation in 114 cases. A considerable number of case studies are included. He concludes that the principal indication for the Steinach operation is premature or physiological old age. In 77% of the cases it has been more or less definite, sometimes striking results in alleviating symptoms of senility, thus prolonging the active period of life. These results can be obtained only if the correct technic is used and a definite indication insisted upon, and under these conditions the procedure is definitely harmless. Where no reason exists to preserve the procreative ability of the patient, a bilateral operation is preferable. The results last several years. Functional impotence is only an indication: (a) when it is one of the symptoms of senility (then senility is the real indication); (b) when endocrine gonadal deficiency can be assumed as a cause; (c) as a last resort after all other treatments have failed.—R. G. H.

Vasectomy in a dog (Un interessant resultat de vasectomie chez un chien). Berganer ('V.), Comp. rend. soc. de biol. (Par.), 1925, 93, 1575-1576.

Sectioning of the left deferent canal in a 14-year-old dog was followed in 4 weeks by disappearance of a central cataract and of a cough, improvement in sight and general physical condition and increase in weight and activity. Four months later the animal died of pulmonary edema. The pH of the blood and stability of the serum colloids (Ruzicka-alcohol precipitation method) were determined throughout the experiment. There was no appreciable change in pH. An increase in the amount of alcohol required to produce cloudiness indicates an increased stability of the colloids which the author interprets as due to increase in metabolism following the activation of the pubertal gland.—R. R. Durant.

Interstitial gland cells in the human ovary. Lewin (B. D.), Am. J. Med. Sc. (Phila.), 1926, 171, 518-520.

Among 43 pairs of ovaries from psychotic patients, 2 ovaries, each from a different case, showed in the hilum a small island of cells identical in appearance with the interstitial gland cells of the testis. The clinical diagnosis in both cases was "senile psychosis." No functional features were to be correlated with this finding. If the cells exerted "male" influences, the fewness of their number in the presence of general senility, prevented this influence from manifesting itself. The possibility of overlooking the presence of such an island, when the ovary is removed in the usual routine autopsy manner, is pointed out.—R. G. H.

**The female sexual hormone. III. The effect of the cyclic hormone when administered by mouth.** Loewe (S.), Lange (F.) & Faure (W.), *Deutsch. m. Wchnschr. (Berl.)*, 1926, **52**, 310-313; Abst., *Chem. Absts.*, **20**, 1440.

With mice the authors were able to obtain the typical specific effects of the sexual hormone when the oral method was used; the dose required was 20 times the subcutaneous dose. Fractional doses under certain conditions produced an additive effect.

**Specific inhibitory hormone of corpus luteum.** Papanicolaou (G. N.), *J. Am. M. Ass. (Chicago)*, 1926, **86**, 1422-1424; Abst., *A. M. A.*

In experiments performed on guinea pigs, the author found that after complete removal of the corpora lutea the ovulation and estrus return on the eleventh day, while in normal guinea pigs estrus usually returns at the fifteenth or the sixteenth day. These findings indicate that the corpora lutea exert an inhibitory action, suppressing and delaying the process of ovulation in the rhythmic function of the ovary. The author has used this inhibitory function of the corpus luteum as a criterion for studying luteal extracts and especially for the recognition of the specific luteal hormone. Some of the purified extracts have been highly efficient in their inhibitory effect. An unmistakable delay follows each injection of this hormone given in small quantities of from 1 to 2 cc. By giving weekly one injection of from 1 to 2 cc., it is possible to suppress the process of ovulation indefinitely. Through such a procedure, Papanicolaou has been able to suppress ovarian rhythm in several animals for a period of from 2 to 4 months. At the end of this period the injections were discontinued, and ovulation reappeared several days after the last injection. The ovaries of animals killed after long suppression show a complete absence of corpora lutea and a large number of middle sized follicles with a highly congested theca interna. This congestion of the theca interna causes an early atresia and prevents the follicles from enlarging into mature graafian follicles. The old corpora lutea degenerate gradually, and the ovary becomes practically free of luteal tissue. The full growth of the follicles and the process of ovulation are thus suppressed, and the ovary thereby loses its cyclic rhythm. This effect is evidently specific and is caused only by the subcutaneous administration of luteal extracts. Similar extracts prepared from other parts of the ovary (follicular fluid, cystic fluid, ovarian residue) and from other organs (placenta, thyroid, thymus, testes and immature ovaries) in all cases gave negative results. It seems evident that this particular hormone is typical for the corpora lutea.

**Eunochoid adiposo-genital dystrophy (Sur la Clinique et le Traitement de la Dystrophie Adiposo-Genitale Eunuchoidique).** Schere-

schewsky (M.), Rev. franc. d'Endocrinol. (Par.), 1925, 6, 395-407.

The author reports in detail a case of dystrophia adiposogenitalis. By way of treatment a cryptorchid testis of a healthy man was transplanted subperitoneally. Histologically the graft showed deficiency of spermatogenic tissue, but augmentation of interstitial cells. The therapeutic results were nil.—R. G. H.

**Activation of the sexual cycle, development of sex characters, reactivating effect on the senile female organism by ovarian and placenta extract.** Steinach (E.), Heinlein (H.) & Wiesner (B. P.), Arch. f. d. ges. Physiol. (Berl.), 1925, 210, 598-611.

Steinach, in conjunction with his associates, Heinlein and Wiesner, have during the last two years conducted a series of experiments on rats and guinea pigs, with a new stable extract prepared from the ovary and the placenta. It was found that in infantile castrates that had not shown any cycle, two to four injections given every 24 hours produced the onset and normal course of a cycle, which could be reproduced by repeated injections ad libitum. Every experiment was positive. A cycle was shown and proved by daily microscopic examination of the vaginal secretions. The size of the uterus developed in the injected infantile castrates exactly the same as in normal animals. The otherwise atrophic state of the vagina was likewise counteracted and brought to full development. The article gives the exact protocols of the experimental animals and their controls. Castration of fully developed animals normally causes a definite cessation of the sexual cycle while the uterus gradually atrophies. With two to four injections given every 24 hours, animals castrated seven months before had their sexual cycle restored and uterus and vagina remained normal. The extract thus forms a potent substitute for the typical endocrine function of the ovary. In a normal female rat the sexual cycle ceases in the nineteenth to the twenty-second month. Animals were injected when the cycle had definitely ceased for two to five months. In every case the experiment was positive, the cycle reappeared and the senile-atrophic tissue of uterus and vagina was regenerated. For several months the sexual cycle recurred normally and automatically without further injections. Accompanying the restoration of the ovarian function, the restoration of the entire organism and the improvement of the animal's general condition was observed in a very pronounced way: the emaciated animal began to eat again, gain in weight, new hair grew on bald spots and the entire fur became thick and glossy. In albinos the iris distinctly showed better circulation. The senile attitude disappeared. The animals became vivacious, curious and began to clean themselves again. They regained the interest of the males who had entirely ignored them before and normal sexual intercourse was observed. A num-

ber of extract protocols are given. Infantile castrates treated with injections every 48 hours for three weeks showed normal mamillae compared to the atrophic, almost invisible infantile organs of the non-treated control animals. The extract had no apparent harmful influence either in castrated or in normal animals. Other ovarian and placenta extracts on the market were found utterly useless; likewise extracts from other organs, for instance, the liver, prepared according to the same method as the author's extract, had no effect whatever. It will be difficult to standardize the extracts, but it seems as if there is a certain relationship between the weight of the animals and the weight of the amount of extract injected. The extract produces exactly the same results as ovarian implantation. The work of other investigators, as well as Steinach's own experiments bearing on the present subject, are fully discussed in a supplementary chapter.—H. Benjamin.

New researches upon the injection of follicular liquid (*Recherches nouvelles sur les injections de liquide folliculaire*). Watrin (J.), *Rev. franç. d'Endocrinol.* (Par.), 1926, 4, 48.

The injection into immature females of follicular liquid taken from a mature ovary causes intense congestion of the genital tract. The tests made by the author confirm this. The congestive phenomena, sometimes very marked, affect other viscera. They appear promptly and disappear rapidly after the cessation of the injections. Under the influence of these injections one is able to produce a rupture of the vessels of the uterine musculature. In a young girl with depressed menstruation an injection of the follicular liquid made 6 days before the expected appearance of normal menses was followed after 24 hours by the beginning of flow.

Studies in experimental diabetes insipidus. Bourquin (Helen), *Am. J. Physiol.* (Balt.), 1926, 76, 181-182.

Diabetes insipidus has been produced in dogs by exposing the hypophysis and directing an electric cautery into the mammillary bodies. That the effective lesion is injury to the mammillary bodies has been demonstrated by histological examination of the brain stem of nine dogs sacrificed while diabetic and of four others, which were not diabetic, but injured in the region of the base of the hypophysis. The lesion common to all of the first group was injury of the mammillary bodies. In four that was the only lesion. The lesions in the latter group were in the tuber cinereum of two, lateral to the mammillary bodies of two. Dogs can be rendered diabetic repeatedly in this way. If, however, the lesion is severe a diabetes already established is immediately stopped and cannot be produced. Histological examination of the brain stem of eight animals subjected to this type of experiment showed complete destruction of the mammillary bodies. Diabetes insipidus is, therefore, an irrita-

tive and not a deficiency phenomenon. It is entirely independent of the hypophysis. A group of four dogs was hypophysectomized and typical diabetes produced. In a second group of four dogs hypophysectomy was successfully performed without causing diabetes insipidus. The cause of the polyuria is still undetermined. It is not a primary thirst phenomenon as some claim, for typical diabetes is produced in dogs deprived of water after the operation. It is not due to an increase in blood chlorides, as others claim, for in 14 of 16 dogs, in which chlorides were determined under standard conditions before and after diabetes insipidus was produced, the diabetic blood contained the same amount as did the normal blood.

Action of hypophyseal extracts upon intestinal peristalsis and constipation (Action des extraits post-hypophysis sur le peristaltisme intestinal et sur la constipation). Carnot (P.) & Terris (E.), Paris M. J., 1926, 16, 333-337.

The peristaltic action of the extract from the posterior lobe of the hypophysis is shown clearly under examination with the fluoroscope. It is marked by colonic contractions and a series of copious evaculations, completely emptying the colon. This action may be graded by various ways of injection and various doses following clinical indications and contra-indications. By vein the most energetic, most vigorous but most violent results are secured. In cases of occlusion, of intestinal paresis and of dyschesia of the sphincter it is especially useful. It is not to be used with a hypersensitive or an organically diseased colon. Intra-muscular injection is more convenient and gives remarkable effects, but is less energetic. They usually are adequate in cases of chronic intestinal stasis. Subcutaneous injections are still less effective. Simple ingestion is most convenient and gives excellent results in habitual constipation. It reinforces intestinal tonus and permits re-education of the musculature of the terminal part of the intestine.—R. G. H.

The action of pituitary extract administered by the alimentary canal. Knaus (H. H.), Brit. M. J. (Lond.), 1926, 1, 234-235.

In the investigation described cats were used as the experimental animals. The author states that when pituitary extract is administered at any part of the alimentary canal—mouth, stomach, small intestine, rectum—pressor action is never observed. When pituitary extract is introduced into the stomach or small intestine, it exerts no influence on uterine muscle. When the extract is administered by mouth, after a latent period of about eight minutes, it exerts a marked action on the uterus, increasing both the tone and automatic movements. The oxytocic substance is therefore absorbed. The rectum absorbs the oxytocic substance also, although absorption is probably not so complete as with administration by mouth.

**Experimental studies on growth. XVIII. Further experiments on the influence of tethelin upon the growth and longevity of the white mouse.** Robertson (T. B.) & Ray (L. A.), Australian J. Exper. Biol. & M. Sc. (Adelaide), 1925, 2, 173-188.

The authors have devised a new technique for the comparison of curves of growth. This consists in plotting the average weights of the animals at different ages not as a series of points, but as a series of areas within which the true values are as likely as not to lie. These collectively constitute a ribbon-shaped area, of which the center at any age is the experimentally ascertained average weight and the vertical width is twice the probable error of the average. Any curve lying outside this area will then represent the growth of some distinctively different group of animals. If two areas overlap for a considerable proportion of their extent, then, during that period, they represent the growth of identical animals. This technique was applied to the further investigation of the effects of tethelin upon the growth and longevity of mice. Previous researches had shown that if tethelin be administered in dosage of 4 mg. per day by mouth, administration during a considerable proportion of the life of the animals leads to the production of small animals which are unusually heavy for their size, a condition reminiscent of acromegaly in human beings. The duration of life is greatly extended, namely, about 100 days, or between one-sixth and one-seventh of the average life-duration of normal animals. If, however, the administration be limited to 8 weeks, from the fifth to the thirteenth inclusive, so that it is discontinued before sexual maturity has been attained, then the growth of the animals, which is at first retarded, is subsequently much accelerated, so that a veritable gigantism is ultimately attained, the average treated animals exceeding the average normals by as much as 25% in weight. Life-duration is not increased. In the present experiments the effect of brief pre-adolescent administration of tethelin was again investigated, the dosage being 4 mg. per day, administered subcutaneously. The results confirm those previously obtained when the tethelin was administered by mouth, but the excess of weight attained was not so great, only 13% above the average, although it lay far outside the range of probable error. On the other hand, the life-duration was greatly increased, almost as much as in previous experiments in which administration was continuous. The effects of hypodermic administration for a brief pre-adolescent period are, therefore, of a character intermediate between those obtained in response to oral administration for a like period and those obtained in response to oral administration for a more prolonged period.—Author's Abst.

**Diabetes insipidus (A Propos d'une Observation de Diabète Isipide).**  
Sabrazés (J.), Rev. franç. d'Endocrinol. (Par.), 1926, 4, 12-23.

The author presents in detail the case history of a subject of diabetes insipidus who did not react at all to whole gland hypophysis treatment by mouth. So far as urine output was concerned, injections of posterior lobe extract had little influence, but they did relieve the intolerable sense of thirst and led to a feeling of euphoria instead of the depressions to which the patient was subject.

—R. G. H.

**Pituitary extract to initiate labor at term.** Tholen (M. H. G. A.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1926, 1, 526-530; Abst., J. Am. M. Ass., 86, 1592.

Tholem gave an intramuscular injection of a small dose of pituitary extract to forty-eight women who were waiting for labor at term, usually after rupture of the bag of waters. Labor pains followed in from half an hour to an hour in 76% of the primiparas and 77% of the multiparas. In five cases requiring premature delivery, the pituitary treatment had no apparent effect. In those cases in which only false labor pains followed the pituitary extract, a sedative was injected at once. The pituitary extract was preceded by castor oil, and the injection was repeated once or twice. The fetal heart sounds were constantly supervised, and no untoward by-effects were observed in either mother or child.

**Variations in the blood sugar content following the administration of insulin.** John (H. J.), J. Lab. & Clin. M. (St. Louis), 1926, 11, 548-560.

Observations on the change of the blood sugar level in diabetic patients following repeated doses of insulin given intravenously during the day, hourly (or more) fluctuations and the same routine on several subsequent days on the same patient. The results are shown in a series of graphic charts over periods of 7 to 21 hours. The cases studied were of varying severity of diabetes, and on a standard dietary routine of gm. 100-60-128-1800 (C-P-F-Cals) so that the only variable was the insulin which was given in uniform and also in varying doses, in one, two or more hours during the day. In one coma case 20 units of insulin was given hourly for 11 hours and bi-hourly for 10 hours more. There is no absolute regularity in the fall of blood sugar after insulin. The degree of drop varies in the same individual on subsequent days on an identical routine. The angle of the fall varies from day to day, or there may be even a rise of blood sugar after such a dose, due no doubt to the post-prandial rise of blood sugar not being adequately counteracted, though the general rule is a drop of blood sugar after insulin. When the insulin dosage was varied it did not necessarily follow that the larger the dose the greater the fall, for the reverse was often the case. Frequent small doses of insulin accomplish more than a single equivalent dose; such an apparently cumula-

tive effect is independent of the size of the doses. Several insulin reactions were recorded, these happening at no marked hypoglycemic, in fact some at a marked hyperglycemic, level. Large doses of insulin were given bi-hourly, 20 units throughout the day with a continued blood sugar level between 68 and 52 mg. per 100 cc. without producing any reaction.—Author's Abst.

**The possible relationship between acromegaly and diabetes.** John (H. J.), Arch. Int. Med. (Chicago), 1926, 37, 489-511.

Experience with the two cases that are reported, in which diabetes was associated with acromegaly, and a study of the literature led John to conclude that, in general, hypopituitarism is accompanied by an increased carbohydrate tolerance and hyperpituitarism, by decreased tolerance, but this is not an absolute rule. In the majority of cases of so-called diabetes associated with acromegaly that have been reported in the literature, especially in older cases, the diagnosis of diabetes was made on the basis of urine examination only. Since glycosuria does not always indicate diabetes, this should be borne in mind in evaluating these reports. In most reported cases and in the two here reported, the onset of acromegaly preceded the onset of diabetes by many years. The treatment of diabetes associated with acromegaly does not differ from the treatment of the ordinary case, and the response of the former type of case does not differ from that of the ordinary cases. Patients in whom diabetes is associated with acromegaly if not controlled are as subject to acidosis and coma as the ordinary case. Hypersecretion of the posterior part of the pituitary gland seems to produce hyperglycemia and glycosuria. Whether this is the predisposing factor is not certainly established; the incidence of diabetes in acromegaly is rather high, but, whatever the primary factor, the metabolic disturbance is due to a decreased insulogenic secretion. It may be that the factor that produces hyperpituitarism may also have some influence in producing the decreased insulogenic function which brings about diabetes. Diabetes is always due to the same immediate factor, namely, a diminution of the insulogenic function and whether it is or is not associated with pituitary dysfunction, its course does not vary and the same treatment is indicated as in the ordinary case.—R. G. H.

**Absorption and insulin (Zur Resorptionsbeschleunigung Durch Insulin).** Koref (O.), & Mautner (H.), Klin. Wchnschr. (Berl.), 1926, 5, 191.

These investigators found that the gastro-intestinal tracts of rats which had received insulin were empty, while those of controls were full when the animals had been fed water, milk or an 8% solution of magnesium sulphate. The animals to which insulin was administered were also more susceptible to poisoning by alcohol

than the controls. If curate was fed 2 hours after the injection of insulin the animal showed typical symptoms in about one-quarter of an hour.—E. Larson.

Note on a rapid and simple method of preparing a highly active pancreatic secretion solution. Luckhardt (A. B.), Barlow (O. W.) & Weaver (M.), Am. J. Physiol. (Balt.), 1926, 76, 182.

The first 100 to 150 cm. of a dog's intestine are excised and the intraintestinal contents removed by passing a stream of tap water through the isolated loop. One hundred to 150 cc. of 0.2% to 0.4% HCl acid are now introduced into the loop and the ends closed with hemostats. The loop with acid contents is either incubated at body temperature or allowed to remain at room temperature for 10, 30 or 45 minutes. Ten minutes' extraction at room temperature usually suffices. At the end of that time the clear or straw colored content of the loop is filtered through cotton (or filter paper) to remove small flecks of desquamated mucosa. The filtrate is now ready for intravenous injection. On intravenous injection of 5 to 10 cc. (10 to 14 kgm. dog under barbital-sodium anesthesia) a copious secretion of pancreatic juice ensues comparable often in quantity to that prepared by the prolonged method of Bayliss and Starling. The earlier such extractions are carried out following excision of the loop of gut from the animal, the less vasodilatation is seen following intravenous injection. We have prepared some extracts with pronounced secretagogue action which were virtually devoid of vasodilatins. Both vasodilatin and secretion dialyze through celluloidin sacs. When kept in brown bottles under toluol in the ice box, the preparations made by the method just described seem to lose their secretagogue action more rapidly than those preparations made from the mucous membrane by the usual process of maceration, grinding with sand and boiling with 0.4% HCl. The vasodilatin action persists, however, indicating anew that the secretagogue action of pancreatic secretin solution is not due solely to the vasodilatins almost invariably present in them.

Raw pancreas in diabetes mellitus. Neve (E. F.), Brit. M. J. (Lond.), 1926, i, 476.

A case report is given of a male, 16 years old. No blood sugar determinations were made. The urine showed 12% sugar at the time observation was begun. Allen treatment reduced the sugar to 4%. The continued use of insulin failed to maintain a low level. Administration of 2 to 3 oz. daily of raw pancreas gave sugar-free urine in 4 days. The patient was discharged a month later greatly improved.—C. I. Reed.

Influence of thymus extirpation on growth and the endocrine organs  
(*Über den Einfluss der Thymektomie auf den Gesamtorganismus*)

und auf die Drüsen mit innerer Sekretion insbesondere die Epiphyse und Hypophyse). Lindeberg (W.), Folia Neuropathologica Estoniana (Dorpat), 1924, 2, 42-108.

The author carried out an extensive series of experiments (thymectomy) on dogs, cats, goats and pigs. Among other, the following results were noted: within the first month there appeared retardation in weight, dentition was delayed, bone growth impeded, rachitic changes were noted, there was muscle weakness and reflexes were augmented. Among the internal organs the most marked changes were noted in the brain, pineal, adrenals and liver. The pineal remained almost microscopic in size, the adrenals and liver were enlarged. The author regards these changes as proof of the endocrine function of the thymus. The literature is somewhat extensively reviewed.—R. G. H.

**Blood sugar in status thymicolumphaticus.** Maclean (Aubrey B.) & Sullivan (Ruth C.), Am. J. M. Sc. (Phila.), 1926, 171, 659-669.

The blood sugar values in 3 cases of status thymicolumphaticus were found to be low (42, 52, 57 mg. per 100 cc.). In one case of suprarenal hemorrhage a blood sugar of 25 mg. per 100 cc. was found. In 6 cases of convulsions produced by conditions other than status thymicolumphaticus the blood sugars were normal or increases above normal. In 6 cases of enlarged thymus shown by roentgenograms the blood sugar in 5 cases was within normal limits and one very slightly decreased. In 6 cases where the blood sugar was determined within half an hour before death on patients with diseases other than status thymicolumphaticus, the values were normal or above normal. Acute suprarenal insufficiency is suggested as the immediate cause of sudden death in status thymicolumphaticus.—R. G. H.

**Hyperthyroidism treated by x-rays.** Barclay (A. E.) & Fellows (F. M.), Lancet (Lond.), 1926, i, 593.

A report is made of the results in 300 consecutive cases in private practice, 63.3% of which were pronounced cured and 25% definitely improved. Secondary conditions, such as cardiac disturbances, were of course not affected by the treatment. The smallest number of treatments effecting a cure was 6, the average 20. One-third of an erythema dose was given twice a week. Results are believed to be permanent. Of the total number of cases, 260 were females, 40 males. The greatest age incidence was between 30 and 50 years. Goiter was present in 75% of the cases, exophthalmos in 68%. The authors believe the basal metabolic rate determination inferior to observation and physical examination as a means of diagnosis. In 10 cases, diabetes was coincident.

—C. I. Reed.

**Tumors of lateral aberrant thyroids.** Billings (A. E.) & Paul (J. R.), Bull. of the Ayer Clinical Laboratory of the Pennsylvania Hospital, 1925, 9, 27; Abst. Ann. Clin. Med., 4, 688.

The authors report a case of papillary adenocarcinoma of a lateral aberrant thyroid and assemble 34 other cases from the literature. They find that these cases present a number of common features. In the great majority the tumor was found in the central portion of the neck beneath the sternomastoid muscle; in 6 cases it was localized close to the angle of the jaw, and in 6 in the supraclavicular fossa. In most of the cases the aberrant thyroid tissue nodules were multiple; in several instances they were noted on both sides of the neck. Twenty-six cases were in females, 6 in males, and no record of the sex was given in 3 instances. The average age at which surgical attention was drawn to the case was 34 for women and 42 for men. The youngest was a girl of 12 and the oldest a woman of 60. In 8 cases a definite malignant neoplasm was recorded as occurring in patients under the age of 30. The pathologic diagnoses varied from thyroid tissue, cystic thyroid to cystadenoma and adenocarcinomas. There is a pronounced tendency for lateral aberrant thyroid tissue to give rise to papillary adenoma and adenocarcinoma, as contrasted to the median or lingual aberrant thyroid which rarely becomes malignant.

**A clinical and pathological study of fifty-five malignant neoplasms of the thyroid gland.** Simpson (W. M.), Ann. Clin. Med. (Balt.), 1926, 4, 643-667.

The results of a clinical and pathological study of 55 cases of thyroid malignancy are reported. Fifty were carcinomas, 5 were sarcomas. An incidence of 4.03% of thyroid malignancy among 1290 surgically removed, non-exophthalmic goiters examined histologically in the period from 1895 to 1925 was found. No instance of carcinomatous transformation of a purely hyperplastic (exophthalmic) goiter was encountered. In every case there was an associated preexisting simple or adenomatous (endemic) goiter. Seventy-two per cent of the malignant thyroid neoplasms occurred in women. In three-fourths of the cases studied the malignant new growth appeared after the thirty-fifth year. Over 60% of this series were unsuspected carcinomas, the correct diagnosis being made only after histological examination. This fact emphasizes the necessity for pathological examination of all extirpated thyroid tissue. Clinical signs of hyperthyroidism were present in approximately one-half of the carcinoma cases. Every hard nodule in the thyroid gland of a person above thirty should be viewed with suspicion as regards malignancy. The frequency with which signs of hyperthyroidism are likewise present provides a second excellent reason for their surgical removal. The most important clinical evidence of early malignancy is a history of relatively rapid

increase in size and hardness in a previously quiescent or slowly growing goiter, particularly in a person over thirty years of age. Radiating neuralgic pain is a common early symptom. Metastasis is common in the advanced stages. The lungs are most often involved, while bone metastases are next in order of frequency. Many thyroid carcinomas are of unusually slow growth. The traditional five-year "danger period" is insufficient. Recurrence after five years is common. An unnecessarily ponderous classification of malignant neoplasms of the thyroid gland has arisen during the past half-century. Many of the terms used describe only minor histological variations, or are in themselves contradictory. It was found quite sufficient to divide carcinomas into three types, on the same basis used in classifying epithelial malignancy arising elsewhere in the body. This classification, based on the morphology and growth characteristics, is found to be in close agreement with the clinical aspects of thyroid malignancy. Medullary carcinomas make up 36% of the cases of malignant epithelial new growth studied. These neoplasms grow with the greatest rapidity, and usually terminate fatally in from one to four years. Recurrence and metastases are common. Those medullary carcinomas in which growth is restricted to a single adenoma offer a more encouraging outlook. Sixty per cent (30) of the carcinoma cases are designated adeno-carcinomas. Twenty-five (83%) of these definitely arose in adenomas, and it is quite probable that the remaining 5 had similar origin. Those adenocarcinomas which are restricted to a single adenoma (malignant adenomas) offer a more hopeful prognosis than those in which the malignancy is not thus limited. Not one of the "malignant adenomas" was diagnosed clinically. Most of these were removed for the relief of toxic symptoms. Scirrhous carcinoma was encountered but twice (4%). Neither case was diagnosed prior to operation. This type grows more slowly than the other type. The so-called "carcinosarcomas" are probably scirrhous carcinomas with an exuberant stroma reaction. Any form of thyroid malignancy may originate in aberrant thyroid tissue. Likewise, any pathological change possible in the thyroid gland, proper, may occur in the thyroid tissue of complex teratoid tumors of the ovary ("dermoid cysts"), sacrum, or elsewhere. We have encountered 2 carcinomas arising in the thyroid tissue of complex ovarian teratomas. Sarcomas of the thyroid gland conform in their growth characteristics to those arising elsewhere in the body. Sarcomas are but one-tenth as frequent as carcinomas in the material reported.

# Endocrinology

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## THE INCREASE OF VOLUNTARY ACTIVITY OF OVARI- ECTOMIZED ALBINO RATS CAUSED BY INJECTIONS OF OVARIAN FOLLICULAR HORMONE.

EDWIN P. BUGBEE AND ALFRED E. SIMOND

From the Medical Research Laboratories of Parke, Davis & Company  
DETROIT

Wang (1923) and Slonaker (1924) have shown that female rats are most active when in the prime of sexual life. Before puberty, and after the changes in the ovaries due to old age have begun, the female rats are much less active. Wang showed in 1923 that this restless activity was due to a stimulus arising from the internal secretion of the ovaries. By removing both ovaries he found the activity was reduced 90 to 95 per cent. During pregnancy, pseudo-pregnancy, and lactation the great restlessness was not present.

Male rats are not nearly as active as female rats, according to Slonaker, Wang, Hoskins, Durrant and Hitecock. Wang, Richter, and Guttmacher (1925) made ovarian transplants into castrated male rats and, in the cases in which the transplants lived, increased the activity of the male rats to the same degree as is normal for female rats. These transformed males showed even the cyclic increase and decrease of activity which Wang

(1923) and Slonaker (1924) have described as characteristic of the female during oestrous cycles.

Durrant (1925) tried to cause increased activity of ovariectomized rats by feeding them glycerine extracts of hog ovaries. The results were negative, probably due to the fact that extracts of ovarian follicular hormone have little effect when given by mouth, as Allen and Doisy (1923) have reported. Glycerine extracts of whole ovaries will cause oestrus in spayed rats when injected subcutaneously, as has been demonstrated in this laboratory.

If ovarian transplants will cause increased activity in castrated male rats, it seemed almost certain that a potent preparation of ovarian follicular fluid, which was known to cause oestrus when injected into spayed rats, would also make them restless and more active. We became interested in this problem in 1924, for we hoped this would furnish a means of standardizing the potency of extracts of ovarian follicular fluid which we were making at that time in co-operation with our colleague, Mr. Adrian Thomas. We have made several experiments in the intervening two years and have demonstrated that preparations of ovarian follicular fluid do increase the activity of ovariectomized rats. These experiments must run over several months to be complete and convincing. We have not been able to report this work before now because accidents have happened to our rats and interrupted the experiments. In the first experiment, in which one of our earlier extracts containing preservative was injected, the dose of the preservative was great enough to kill the rat. In another experiment the normal control died of pneumonia before the experiment had been completed.

The experiment reported in this paper is subject to the just criticism that only one rat is used to show the effects of injections of the ovarian follicular hormone. We can say, however, that the results reported are confirmed in every detail by the other experiments which we have made during the last two years.

The voluntary activity, which is an index of the restlessness of rats, has been determined by counting the number of revolutions which the rats turn revolving cages in which they are kept.

The revolving cages which we have used in these experiments are similar to those described by Stewart (1898) and Slonaker (1907, 1908). They differ in size and arrangement

from those used by Richter (1922), Wang (1923), Durrant (1924, 1925), Hoskins (1925, a, b, c) and Hitchcock (1925).

The cage proper is cylindrical, 18 inches in diameter and 18 inches long. The ends are made of galvanized sheet iron and the periphery is of wire cloth, 4 meshes to the inch. The cage is mounted on brass bearings and turns very easily on a fixed axle. At one end of the cage is a small eccentric against which bears a pin projecting from the arm of a Veeder revolution counter. Revolutions of the cage in either direction are thus recorded additively by the revolution counter. From the stationary axle are suspended the nest box and water dish and food dish. The

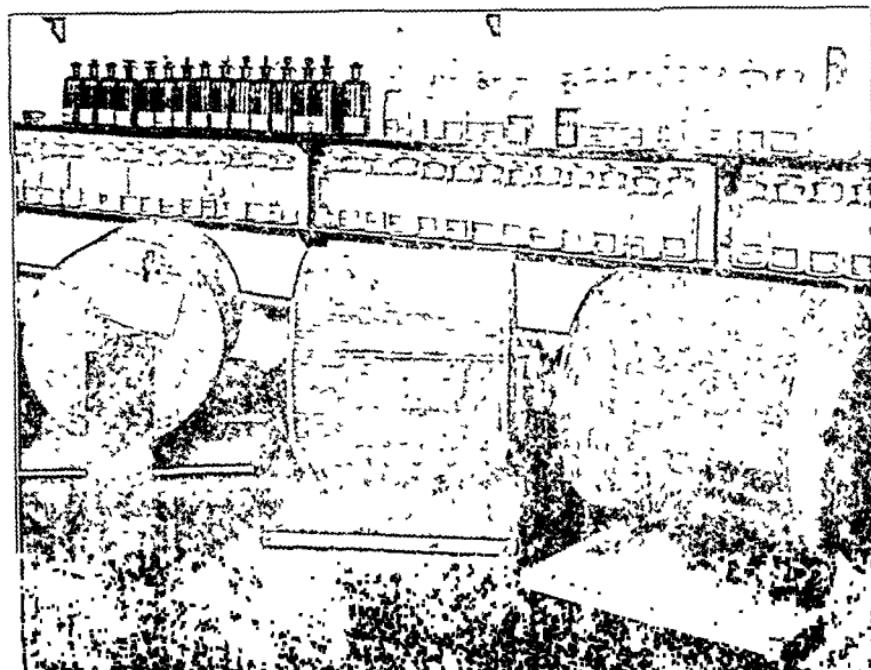


Fig. 1 Revolving cages with revolution counters to record running activity of rats

nest box is made of galvanized iron 10 x 6 x 3 inches. The food and water dishes are also made of galvanized iron 3 x 3 x 1½ inches. Figure 1 is a photograph of three cages grouped so as to show the details of construction.

During the experiment the three cages are placed end to end on a table. They are kept in the laboratory in which a fairly uniform temperature between 20° and 30° C. is maintained. The fact that three men are moving about the laboratory during

working hours seems to make no appreciable difference, as the rats sleep most of the daytime and do their running at night. The rats have access to food and water at all times. The food is the Sherman rat ration (Sherman and Campbell, 1924), or the similar formula given in the U. S. P. X., page 469, which consists of whole wheat flour 66 per cent, whole milk powder 33 per cent, and sodium chloride 1 per cent.

#### EXPERIMENTAL PROCEDURE

Three healthy female rats of practically the same size and the same age (about 60 days) were put in the revolving cages. They were kept under observation for twenty days, and the numbers of revolutions that they turned the cages were recorded for each twenty-four hours. The two rats which were most active in the 20-day period were spayed and the other was kept as a normal control. After another observation period of twenty-two days the less active spayed rat was chosen for injections of ovarian follicular hormone and the more active was kept without treatment as a spayed control.

Injections of one of our preparations of ovarian follicular hormone were given at proper intervals so as to cause oestrus in the spayed rat every 4 or 5 days. In this way the spayed rat was kept going through regular oestrous cycles, the same as a normal female rat. The preparation of ovarian follicular hormone used was the same throughout the whole experiment. It was made by our colleague, Mr. F. H. Tendick, and is an aqueous, colloid solution of the emulsoid type. It is put up in 1 c.c. ampoules and is sterilized in the autoclave. Each cubic centimeter is the extract from 6 cc. of fresh follicular fluid, from hog ovaries. Each cubic centimeter contains 8 Rat Units of activity, one Rat Unit being the minimal amount necessary to cause typical oestrus in a spayed rat of 140 grams weight. This is the Rat Unit originally adopted by Allen and Doisy (1923, 1924). As mentioned in a previous article (Bugbee and Simond 1926), we believe our aqueous solution is more effective in causing oestrous in spayed rats when given in eight injections, 4 daily on two successive days.

By examination of vaginal smears to determine the stage of the oestrous cycle we have noted that the greatest number of revolutions of the revolving cage is recorded the morning after

the rat has passed through stage 2 of the oestrous cycle. This means that a female rat is most restless and active when she is in heat. This fact has previously been recorded by Wang (1923), Slonaker (1925), Durrant (1925), and Hitchcock (1925).

Figure 2 is the record of activity of the normal female rat, No. 227, from about 60 days to about 218 days of age. It is characteristic of a normal female rat and shows the cyclic variation of activity.

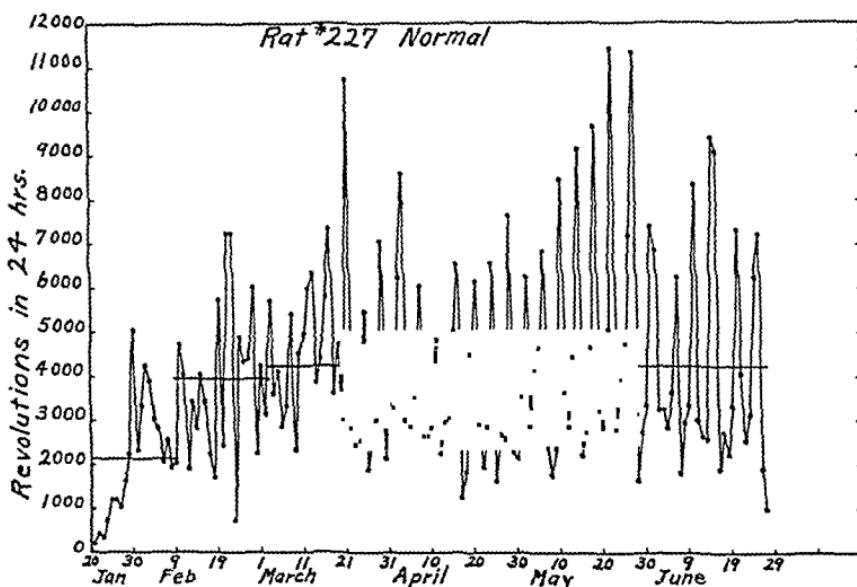


Fig. 2. A record of the voluntary activity of a normal female white rat from about 60 to 218 days of age.

Figure 3 is a record of the activity of a rat (No. 228) of the same age as the other two rats, before and after ovariectomy. It will be noted that the record of activity of the spayed rat does not show the extreme regular cyclic variations that the record of the normal rat shows. This was the most active rat of the three before ovariectomy, and did not show as great a reduction in activity after ovariectomy as is usual according to Wang (1923) and Durrant (1925). *Table I* shows the periods into which the experiment is divided and the special treatment which each rat received during these periods. The average daily revolutions in each period are shown. The number of Rat Units of ovarian follicular hormone injected into rat No. 236 are given in detail.

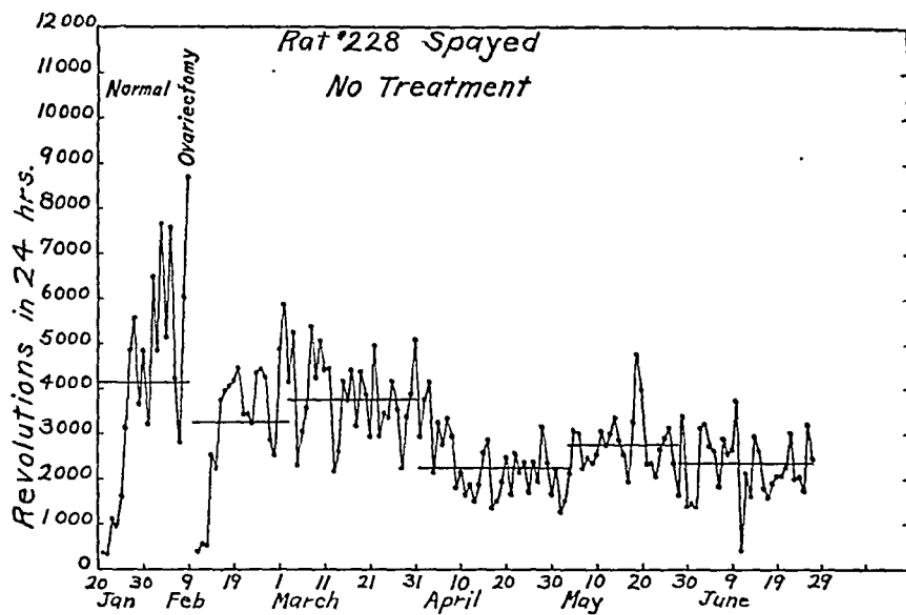


Fig. 3. A record of the voluntary activity of a white rat before and after ovariectomy.

TABLE I.

	Jan. 20 to Feb. 9 (20 days)	Feb. 10 to Mar. 3 (22 days)	Mar. 4 to Apr. 1 (29 days)	Apr. 2 to May 4 (33 days)	May 5 to May 28 (24 days)	May 29 to June 27 (30 days)
Rat No. 227 (Av. rev. per day)	Normal No treat. 2127	Normal No treat. 3954	Normal No treat. 4230	Normal No treat. 3845	Normal No treat. 4983	Normal No treat. 4206
Rat No. 228 (Av. rev. per day)	Normal No treat. 4145	Spayed No treat. 3290	Spayed No treat. 3768	Spayed No treat. 2246	Spayed No treat. 2780	Spayed No treat. 2330
Rat No. 236 (Av. rev. per day)	Normal No treat.	Spayed No treat.	Spayed 3-2 inj. 4R.U. 3-3 " 4R.U. 3-6 " SR.U. 3-12 " 4R.U. 3-13 " 4R.U. 3-17 " 4R.U. 3-18 " 4R.U. 3-23 " 4R.U. 3-24 " 4R.U. 3-29 " 4R.U. 3-30 " 4R.U.  4SR.U.	Spayed No treat.	Spayed 5-3 inj. SR.U. 5-4 " SR.U. 5-7 " SR.U. 5-8 " SR.U. 5-11 " 16R.U. 5-12 " 8R.U. 5-17 " 16R.U. 5-18 " 16R.U. 5-21 " 16R.U. 5-22 " SR.U. 5-25 " 16R.U. 5-26 " 16R.U.  144R.U.	Spayed No treat.

Horizontal Lines—Averages of revolutions per day during the periods over which they extended. The periods are explained in Table I.

Rats not in revolving cages for 24 hours after ovariotomy.

Revolutions not read on Sunday, Feb. 21, so the figures for Feb. 21 and 22 are the average for two days.

All three rats are about the same age and weight.

Figure 4 shows the record of activity of rat No. 236 before and after ovariectomy. It was the same age and size as the other two rats. It will be noted that it showed a decrease of 58 per cent in average daily activity in the 22 days following ovariectomy. In the next period of 29 days injections of ovarian follicular hormone were given at intervals and in dosage as shown in Table I. As it takes from 24 to 48 hours for oestrous to be produced by the ovarian follicular hormone, and

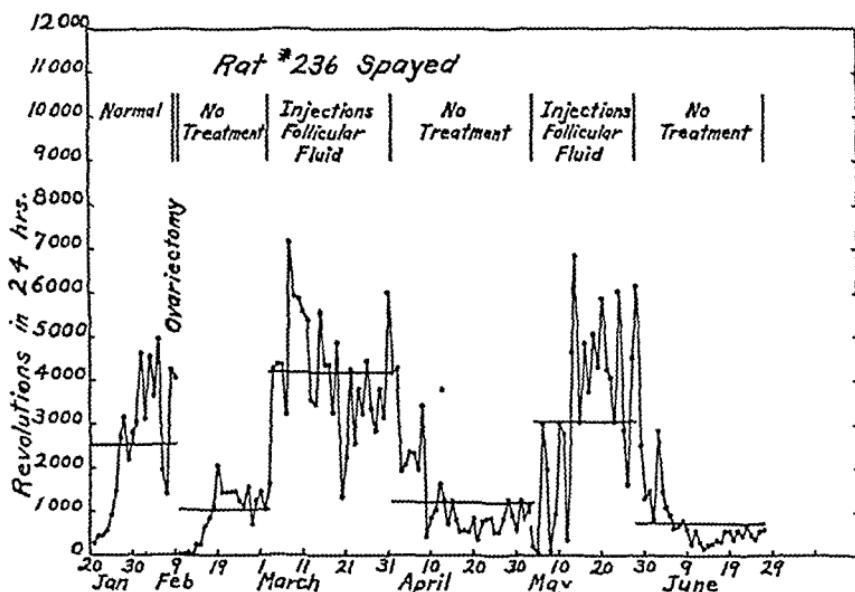


Fig. 4. A record of the voluntary activity of an ovariectomized white rat which received injections of a preparation of ovarian follicular hormone.

because the record of revolutions was read in the morning after oestrus had occurred, we have considered the period of injection to begin 2 days after the beginning of injections. Moreover, the oestrus effects last for 12 hours or more, so we have considered the period of injection to last for 2 days after the last injection was given. In the injection period of 29 days (March 1 to April 1, inclusive) 48 Rat Units of ovarian follicular hormone were injected, as shown in detail in Table I. This caused cyclic variations in activity (Figure 4). The average daily number of revolutions increased from 1,054 to 4,194, an increase of 298 per cent.

Next followed another rest period of 33 days without injections, during which time the activity of the rat decreased to a

low level, an average of 1,210 revolutions per day, a decrease of 71 per cent.

A second injection period of 24 days followed, during which time large doses of ovarian follicular hormone were given. These are shown in detail in Table I. The hormone caused a marked increase of activity in this period, the average daily activity rising to 3,066 revolutions, which was an increase of 153 per cent.

A final rest period of 30 days without injections followed. During this time the activity of the rat sank to the low level of 754 revolutions per day for an average. This was a decrease of 75 per cent.

It will be noted by comparing Figures 2, 3 and 4 that both the normal control and the spayed control showed increased activity during the two injection periods, although not to the same degree as did the rat which was injected. This effect is due, no doubt, to the fact that the three cages were very close together and the two controls were stimulated by hearing the other cage revolving.

Both of the spayed rats were killed at the end of the experiment and carefully examined to see if any traces of the ovaries had been left after the operation. In both animals the uterine horns were atrophied and no traces of ovaries could be found. In rat No. 236, which had received the injections of ovarian follicular hormone, the uterine horns were slightly larger than in the rat which had not had any injections. In this connection it may be mentioned that in another experiment we gave a spayed rat injections of ovarian follicular hormone every week for nine months after ovariectomy and then killed the rat during an artificial heat period and found no apparent atrophy of the uterine horns.

#### DISCUSSION

In the present experiment it will be noted that during the first period of injection 48 Rat Units were given over an interval of 29 days. During the second period of injection 144 Rat Units were given over an interval of 24 days. In spite of the fact that three times as great dosage was used in the second period of injection as had been used in the first period of injection, the reaction was not as great. This demonstrated quite clearly that the activity reaction to ovarian follicular hormone is not a

quantitative reaction, at least we can say with assurance that three times the dosage does not produce three times as much increase in voluntary activity.

The fact that the ovarian follicular hormone does not act in a quantitative manner leads us to believe that it does not stimulate muscles themselves, but rather that it increases the irritability of the whole nervous system. One has only to watch a female rat in heat to observe that she is more irritable and that all her movements are quicker than at other times. In normal heat the basal metabolic rate is not increased in dogs, but the nervous irritability is increased as Kunde (1923) has recorded in the following statement:

" . . . there was no increase in the B. M. R. during rut, but in two of the periods there was a decrease of from 3.4-4%, while the one period shows no change. This precaution should be mentioned in making metabolism determinations on dogs in heat; it was difficult to get Dog No. 1 perfectly quiet at the beginning of the rest period. She seemed unusually alert and ready to respond to the least movement about her."

Evidence bearing on this point is also furnished by experiments in which ovaries have been removed. Such spayed animals are sluggish, but it is doubtful if the basal metabolic rate is reduced by the ovariotomy itself (Lusk, 1925).

Hoskins (1925, a, b, c) has shown that in male rats castration reduces the voluntary activity. It is a common observation in farm animals that castration reduces excitability of the male. Such castrated males, as for example, the horse and the ox, are able to work apparently as well as before operation. In a recent article (Bugbee and Simond, 1926, a) we have reported a castration experiment on a dog which adds evidence to that presented by other investigators that castration in itself does not reduce the basal metabolic rate to any considerable extent.

Gans and Hoskins (1926) have carried this investigation of the influence of the testes down to the muscle-nerve combination in normal and castrated rats. They report that the absolute strength of the muscles is the same in both groups. The total work performed by the castrated animals was considerably less than that performed by the normal animals. Their experiments on the whole indicated that the sluggishness of castrated animals could be ascribed to a lessened efficiency of the muscles. The

castrated animals showed an increased fatigability which could be ascribed to the lessened muscular efficiency, *per se*, but is more likely due to inadequacy of supporting functions, such as circulation or respiration.

This whole subject of the influence of ovaries and testes on metabolic rate, activity, muscular efficiency, body growth, mental development and nervous irritability is extremely interesting both from the standpoint of the solution of some of the mysteries of physiology and also because of its practical value in therapeutic applications to man and lower animals.

At present we have under way an experiment with male rats into which we shall inject ovarian follicular hormone to see if the female hormone will have the same stimulating influence on the male as it does on the sex to which it naturally belongs. Wang, Richter and Guttmacher (1925) have proved that successful ovarian transplants will stimulate activity in castrated male rats. In our experiment we hope to show that it is the hormone contained in follicular fluid which is responsible for this stimulation.

We wish to acknowledge our gratitude to Dr. E. M. Houghton, Director of the Biological Laboratories, for his interest and help which have made it possible for us to carry on this work.

#### SUMMARY

1. Normal female rats, in the prime of life, have periods of greatly increased activity which are coincident with heat periods.
2. These periods of increased activity are not found in ovariectomized rats.
3. The voluntary activity of ovariectomized rats is much less than that of normal female rats of the same age.
4. Injections of extracts of ovarian follicular hormone, in proper dosage and at proper intervals, into ovariectomized rats cause artificial heat periods in which the voluntary activity is increased the same as in normal heat periods in normal rats.
5. Repeated injection of extract of ovarian follicular hormone increase the total voluntary activity of ovariectomized rats during the period of injection, but when injections are discontinued the voluntary activity decreases to its former low level.

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THE EFFECTS OF INJECTIONS OF OVARIAN FOLLICULAR HORMONE ON BODY GROWTH AND SEXUAL DEVELOPMENT OF MALE AND FEMALE RATS

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From the Medical Research Laboratories of Parke, Davis & Company  
DETROIT

In a recent article (Bugbee and Simond, 1926) we reported that injections of ovarian follicular hormone increase the activity of ovariectomized rats. It is of interest to know whether or not this stimulating hormone affects other bodily functions in the same way. It is particularly interesting to know if it stimulates body growth and brings about precocious sexual maturity in young female rats. We have used both male and female rats in this experiment so as to determine whether or not the female hormone exerts any effect on normal males and on castrated males.

EXPERIMENTAL PROCEDURE—FEMALE RATS

Twelve female rats, about six weeks of age, of nearly the same weight, were selected for the experiment. Six of these were ovariectomized. In one week they had apparently completely recovered from the operation. The twelve rats were then grouped as follows:

Series A = 3 normal female rats for controls, not to be given any treatments.

Series B = 3 normal female rats to be given injections of ovarian follicular hormone.

Series C = 3 spayed rats for spayed controls, not to be given any treatments.

Series D = 3 spayed rats to be given injections of ovarian follicular hormone.

The twelve female rats were kept in one cage in which were three male rats about seven months old.

Sexual maturity of the female rats was to be judged by the date of birth of young. The rats were weighed once or twice

a week. They were given the Sherman rat ration (Sherman and Campbell, 1924), or the similar ration given in the U. S. P. X. page 469, which consists of whole wheat flour 66 per cent, whole milk powder 33 per cent, and sodium chloride 1 per cent.

The rats of Series B and Series D were given subcutaneous injections of ovarian follicular hormone. The preparation was made by our colleague, Mr. F. H. Tendick. It was an aqueous, colloid solution of the emulsoid type. It was put up in 1 c.c. ampoules and sterilized in the autoclave. Each cubic centimeter had the potency of 8 rat units, a rat unit as defined by Doisy, Allen and their associates (1924) being the minimal amount necessary to cause oestrus in a spayed rat of about 140 grams. Each rat was given  $\frac{1}{2}$  c.c. daily, except Sundays, for four weeks so it received 96 rat units in all.

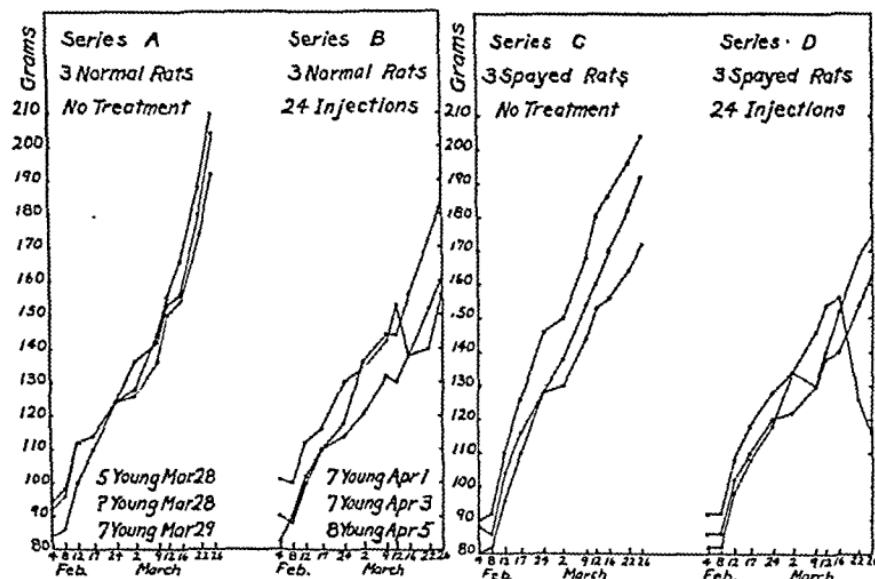


Fig. 1. Weight curves of normal female rats.

Fig. 2. Weight curves of spayed rats.

#### GROWTH OF FEMALE RATS

Figures 1 and 2 show the weight curves of the individual rats grouped in series. It can be noted at a glance that the normal rats which received injections of ovarian follicular hormone (Series B) did not grow as well as the normal rats which did not receive such treatment (Series A). Also the spayed

rats which received the injections (Series D) did not grow as well as the spayed rats allowed to go without treatment (Series C). These individual weight curves show that one rat in each series which received injections (Series B and D) lost considerable weight in the latter part of the experiment. These rats acted sick and on postmortem examination were found to have pneumonia. The injections were probably not responsible for the infection as we have no evidence that such injections lower resistance.

Figure 3 shows the weight curves of the average weights of the three rats in each series.  $B^1$  and  $D^1$  show the weight curves of Series B and D when the sick rats are left out and the

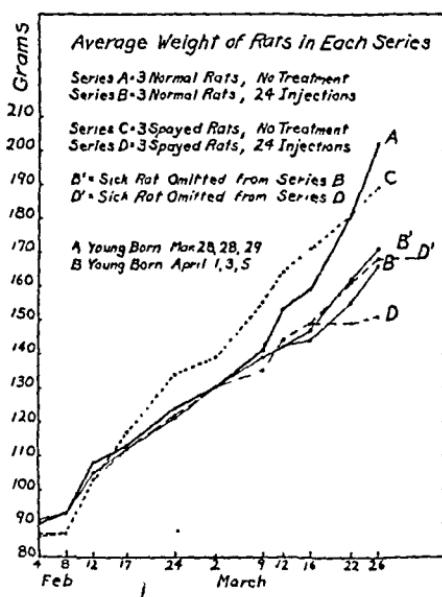


Fig. 3. Weight curves of average weight of female rats in each series.

average is taken of the two remaining rats in each series.

It will be noted that the spayed rats which did not receive any treatment (Series C) showed the highest average weight until the normal control rats (Series A) became pregnant. As pregnancy advanced the weight of the young added to that of the mothers made Series A surpass Series C.

The average weight of the rats which received injections of ovarian follicular hormone was continually nearly equal in the normal females, Series B, and the spayed ones in Series D.

This would seem to indicate that such large doses of ovarian follicular hormone were given to the spayed rats that there was no chance for them to become "fat castrates." It also seems to show that excessive doses of ovarian follicular hormone, when given to normal female rats, causing a condition of hyperovarianism, counteracts the tendency towards obesity.

#### SEXUAL DEVELOPMENT OF FEMALE RATS

The normal rats which did not receive any treatment (Series A) gave birth to young on March 28, March 28, and March 29. The normal rats which received the injections of ovarian follicular hormone (Series B) gave birth to young on April 1, April 3, and April 5. This indicates that the ovarian follicular hormone did not cause precocious development of all parts of the female genital organs. It can be easily demonstrated on immature female rats of 4 weeks of age that injections of ovarian follicular hormone cause opening of the vagina and the changes in the vaginal mucosa characteristic of oestrus. Evidently, however, there is lacking part of the mechanism of reproduction until maturity is reached. This experiment is not extensive enough to warrant the conclusion that the injections of ovarian follicular hormone delayed the development of powers of reproduction.

#### EXPERIMENTAL PROCEDURE—MALE RATS

Twelve male rats of about three weeks of age and of nearly the same weight, were selected for the experiment. Six of these were castrated. In three days they had apparently recovered from the operation and the incisions had nearly healed. The twelve rats were then grouped as follows:

Series A—3 normal rats for controls, not to be given any treatments.

Series B—3 normal rats to be given injections of ovarian follicular hormone.

Series C—3 castrated rats for controls, not to be given any treatments.

Series D—3 castrated rats to be given injections of ovarian follicular hormone.

The three normal males and the three castrated males to

which no treatments were to be given, Series A and Series C, were put in a cage with six female rats about two months old.

The three normal males and the three castrated males to which injections were to be given, Series B and Series D, were put in a cage with six females about two months old. Sexual maturity of the male rats was to be judged by the date of birth of young in their female cage-mates.

The rats of Series B and Series D were given subcutaneous injections of ovarian follicular hormone  $\frac{1}{2}$  c.c. daily, except Sundays and holidays, from November 16, 1925, until February 1, 1926. The preparation of ovarian follicular hormone was

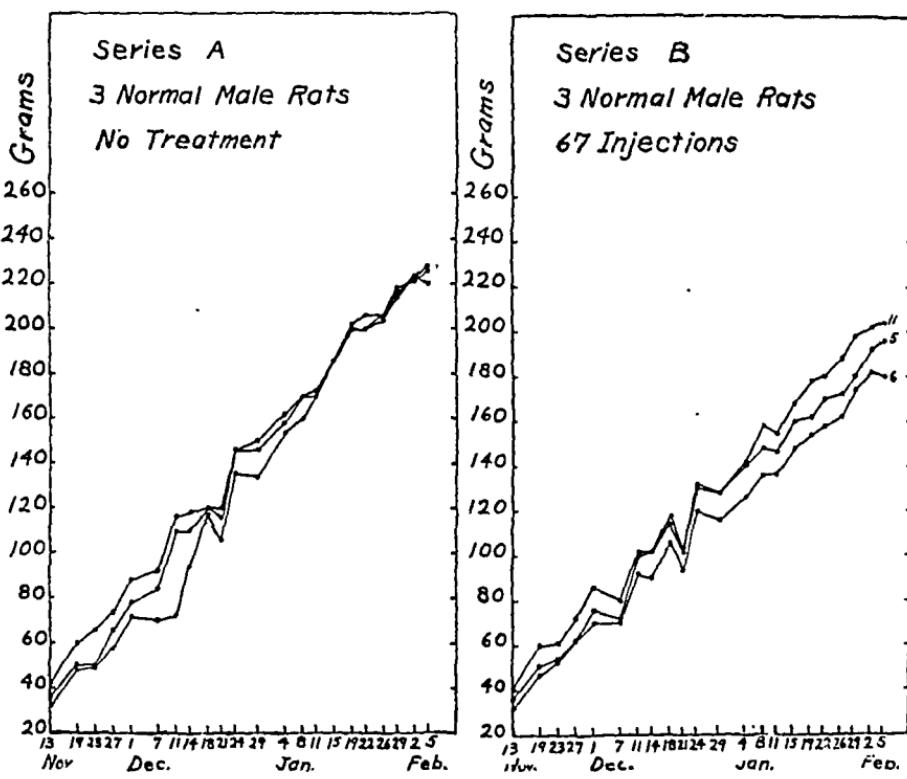


Fig. 4. Weight curves of normal male rats, no treatment.

Fig. 5. Weight curves of normal male rats injected with ovarian follicular-hormone.

similar to that already mentioned. Several lots of varying potency were used but in every case all six rats were given the same preparation at the same time. Each rat received 67 injections having the total potency of 64 rat units.

## GROWTH OF MALE RATS

Figures 4, 5, 6 and 7 show the weight curves of the individual rats grouped in series. It is very apparent from inspection of these curves that the normal male rats which received the injections of ovarian follicular hormone (Series B) did not grow as heavy as the normal rats to which no treatments were given (Series A). The castrated rats which received injections (Series D) are plainly not as heavy as the castrated rats left untreated (Series C).

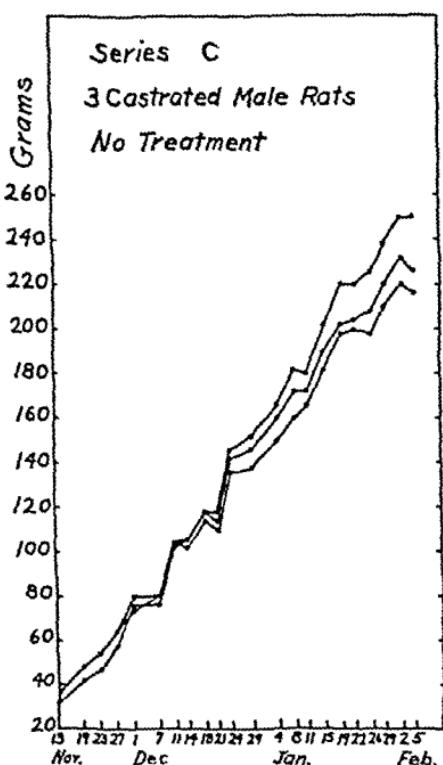


Fig. 6. Weight curves of castrated rats, no treatment.

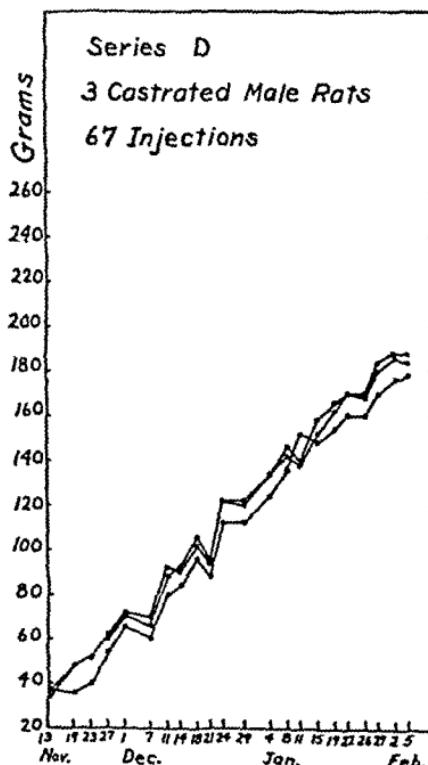


Fig. 7. Weight curves of castrated rats injected with ovarian follicular hormone.

Figure 8 shows the weight curves of the average weight of the three rats in each series. The castrated controls (Series C) are the heaviest of all. Next come the normal controls (Series A). Next come the normal rats which received injections (Series B), and the lowest of all were the castrated rats which received the injections of ovarian follicular hormone (Series D).

## SEXUAL DEVELOPMENT OF MALE RATS

The female cage-mates of the normal male rats, to which no injections were given (Series A), gave birth to young on February 22, 24, 24, March 2 and 3.

The female cage-mates of the normal male rats, to which injections of ovarian follicular hormone were given (Series B), gave birth to young on February 26, March 4, 4, 4, 5 and 12.

Evidently the injections of ovarian follicular hormone did not cause precocious sexual development in the male rats. There is not sufficient evidence, however, to warrant the conclusion that the ovarian follicular hormone retarded sexual development.

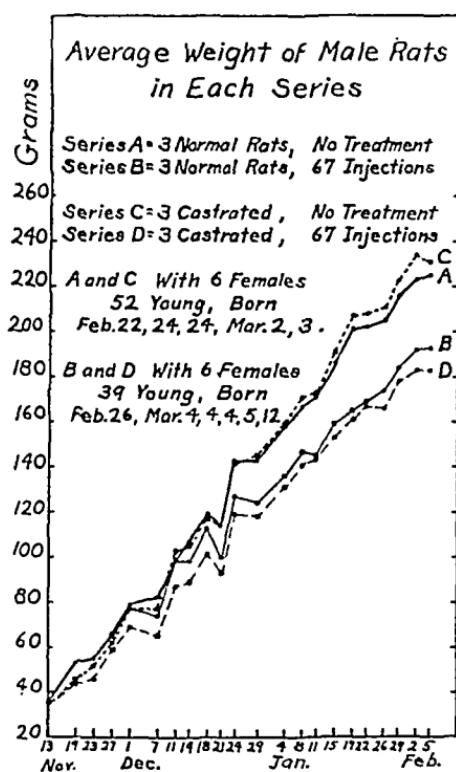


Fig. 8. Weight curves of average weight of male rats in each series.

## DISCUSSION

All the evidence obtained from the male and female rats in this experiment indicates that injections of ovarian follicular hormone into immature rats retards their growth. This is in

harmony with the commonly accepted ideas regarding the influence of the gonads on body growth. It is the usual procedure for the stock raiser to remove the gonads from animals raised for food purposes so that they will grow heavier. A considerable portion of the excess weight is due to deposits of fat in the subcutaneous tissues and other fat storage tissues. We should expect that excessive gonad secretion, or artificial increase by injection, would decrease the amount of fat storage in the body. Wang, Richter and Guttmacher (1925) have shown that castration causes male rats to increase in weight and successful ovarian transplantation causes a loss of the excess weight. As our results agree with theirs one draws the conclusion that the ovarian follicular hormone secreted by the ovarian transplants was responsible for the loss of weight in their rats.

In both parts of this experiment on the effect of the ovarian follicular hormone on sexual maturity as judged by reproduction, it is apparent that young were born to injected females and to the cage-mates of injected males later than to the corresponding controls which did not receive injections. At first thought one might consider that the injections had delayed reproduction. The number of rats used was so small that a definite conclusion is not warranted. It is quite evident, however, that the ovarian follicular hormone does not cause early attainment of reproductive power. Brouha and Simonnet (1925) have noted that injections of ovarian follicular hormone into immature animals cause development of the vagina and uterus but do not cause growth of the ovaries. Allen and Doisy (1923) reported that sexual maturity involving possibly the development of the secondary sexual characters is brought about by the hormone from the follicles but that consummation of maturation is in some way restrained.

Although we have no definite evidence we may surmise that the maturity of the ova is not hastened by injections of ovarian follicular hormone, and that reproduction cannot take place until the ova mature in the normal manner.

Our experiment indicates that the ovarian follicular hormone is not entirely a specific female hormone, for it has an

effect on male rats. It reduced their weight in the same way as it reduced the weight of the female rats.

No evidence was found that the ovarian follicular hormone had any antagonistic action on the male sexual apparatus. Apparently the injected males had normal masculine psychic reactions in the presence of the opposite sex. This evidence makes it seem probable that there is no antagonism between male and female sex hormones.

We wish to acknowledge our gratitude to Dr. E. M. Houghton, Director of Research and Biological Laboratories, for his help and encouragement during the progress of this experiment.

#### SUMMARY

1. Ovariectomy causes young rats to grow heavier than normal female rats.
2. Subcutaneous injections of ovarian follicular hormone cause a loss of weight in normal and ovariectomized female rats.
3. Castration causes young rats to grow heavier than normal male rats.
4. Subcutaneous injections of ovarian follicular hormone cause a loss of weight in normal and castrated male rats.
5. Subcutaneous injections of ovarian follicular hormone do not cause male or female rats to reproduce earlier than normal.
6. Ovarian follicular hormone is not entirely a specific female hormone, for it reduces the weight of male rats in the same way as it reduces the weight of female rats.
7. The conclusion is drawn that the ovarian follicular hormone does not have any antagonistic effect on the male sexual apparatus.
8. It seems probable that the male and female sex hormones are not antagonistic.

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STUDIES OF THE THYROID APPARATUS. XXXVII.  
THE RÔLE OF THE THYROID APPARATUS  
IN THE GROWTH OF THE THYMUS

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INTRODUCTION

The organs which serve as the basis of this study were obtained from the same rats the growth of which in body and in part has been discussed in the preceding papers of this series. Table 1 gives the observed mean weights for the several groups. Table 2 gives the percentage increments of the controls and the tests, and the percentage rate of growth of the tests in terms of that of their controls for each of the age series (23, 30, 50, 65, 75 and 100 days). The charts make possible a visualization of the comparative response. The flat black columns represent control growth (always 100 per cent), while the outline columns represent the growth of the tests in terms of that of their controls (T/C values). The pubertal and post-pubertal retrogression of the thymus in conditions of thyroid and parathyroid deficiency is so extensive that the actual values are not conveniently representable on a chart. Hence the broken columns. The degree of response is not recorded, since the multiplicity of figures is confusing. These can be found in table 2. Notwithstanding the partial inadequacy of the charts in this direction, they do serve to give a visual impression of the various inter-relations.

The normal course of thymus growth has yet to be plotted. This is because the organ is, next to the thyroid, the most sensitive of all the organs of the body to dietary (1) and other disturbances. It reacts thereto in a degree all out of proportion to the reaction of the body as a whole. Its specific variability (the variability uninfluenced by body size and the weight changes of the other glands of internal secretion), is higher than that of any other organ (save the thyroid) so far studied. The value for the male is  $25.70 \pm 1.18$ , and for the female  $21.48 \pm 0.097$ , in the adult (150 day old) albino rat (2).

There is a general belief that the thymus undergoes a normal "age" involution, as distinguished from the "accidental" involution caused by dietary and other disturbances. Exact proof for this belief is lacking. This is because no individual lives a life that is completely free from physiological fluctuations, due to disease or dietary variations, which may well have produced an "accidental" thymic involution of such degree that complete recovery therefrom has been impossible. I do not believe that we ever get at autopsy a thymus which can be considered "normal," in the sense of its having been throughout the life of the individual free from disturbance, to which it so sensitively responds. The only way in which we can get even an approximately true solution of the problem is to study thymic growth in laboratory animals raised under constant optimal dietary and environmental conditions, and continuously free from disease of any kind. The high sensitivity of the organ, the possibility of its recovery from the "accidental" type of involution (1), and the general lack of exact knowledge with regard to its function, would seem to make such a study worth while.

Hammar (3), who has probably studied this question more than any other single individual, states that "the old theory of the age involution has—undergone revision to the effect that the involution does not appear until puberty and that it certainly causes a gradual reduction of the parenchyma, but in such a way, however, that a functioning parenchyma remains as a rule, even in old age." Hatai's (9) analysis of his own data combined with those of Jackson, shows that the thymus progressively increases in weight in the albino rat up to puberty, when involution makes its appearance. My data in table 1 (control groups) show the same thing. Thus the first part of Hammar's conclusion is substantiated.

According to Hatai's curve the thymus undergoes a progressive loss of weight after puberty. This is in general agreement with Hammar's conception of the age reduction in thymic parenchyma. But neither Hatai's material nor that of Hammar satisfies the ideal requirements postulated in the preceding paragraph. For Hatai's data were derived from rats on sub-optimal diets, and Hammar's from individuals subjected to the various vicissitudes of existence.

## GROWTH OF THYMUS

TABLE I  
*The Observed Mean Weights of the Thymus of the Several Groups of Rats*

Age Series	THYROPARATHYROIDECTOMIZED						PARATHYROIDECTOMIZED			
	At Beginning			At End			At Beginning		At End	
	Ref.	Contl.	Test*	Control	Test	Contl.*	Test*	Control	Test	
MALES										
23	0.0828±0.0046	0.0851	gm. 0.0851	0.3194±0.0182	0.1593±0.0150	gm. 0.0850	0.0825	gm. 0.3065±0.0188	gm. 0.1831±0.0132	
30	0.1188±0.0061	0.1162	0.1145	0.2947±0.0222	0.1747±0.0269	0.1180	0.1176	0.3013±0.0160	0.1752±0.0086	
50	0.1989±0.0039	0.1936	0.1921	0.2702±0.0169	0.1308±0.0091	0.1947	0.1908	0.2471±0.0133	0.1513±0.0142	
65	0.2761±0.0134	0.2627	0.2661	0.2418±0.0162	0.1137±0.0159	0.2673	0.2684	0.2912±0.0209	0.1002±0.0118	
75	0.2971±0.0108	0.2847	0.2886	0.2802±0.0158	0.1462±0.0155	0.2908	0.2850	0.2065±0.0170	0.0980±0.0075	
100	0.2380±0.0126	0.2347	0.2330	0.2828±0.0136	0.1564±0.0108	0.2347	0.2293	0.2828±0.0136	0.2090±0.0099	
FEMALES										
23	0.1077±0.0068	0.1042	0.1021	0.2483±0.0107	0.1322±0.0113	0.1078	0.1065	0.2718±0.0152	0.1484±0.0136	
30	0.1131±0.0038	0.1112	0.1100	0.3043±0.0194	0.1312±0.0080	0.1132	0.1112	0.2709±0.0175	0.1825±0.0080	
50	0.2422±0.0105	0.2330	0.2323	0.2092±0.0082	0.1098±0.0101	0.2417	0.2379	0.2346±0.0078	0.1361±0.0060	
65	0.3176±0.0098	0.3090	0.2999	0.2511±0.0133	0.1617±0.0148	0.3103	0.3042	0.2474±0.0090	0.1366±0.0118	
75	0.2792±0.0157	0.2705	0.2668	0.2284±0.0164	0.1056±0.0143	0.2653	0.2658	0.2182±0.0153	0.1305±0.0136	
100	0.2480±0.0161	0.2402	0.2402	0.2602±0.0141	0.1334±0.0110	0.2402	0.2365	0.2602±0.0141	0.1758±0.0103	

"Beginning" values for "Control" and "Test" groups computed according to method referred to in text.

From table 1 (control groups) it is evident, as was pointed out in an earlier paper (5), that under the best conditions so far developed for growing albino rats (6) the thymus, instead of losing, gains weight during the post-pubertal growth period from 100 to 150 days of age. This does not look like an "age" involution. The fact that growth occurred in four separate

TABLE 2

*The Absolute and the Relative Rate of Growth of the Thymus of the Several Groups of Rats*

Age Series	MALES			FEMALES		
	Thyroparathyroidectomized					
	Control	Test	T/C	Control	Test	T/C
23	264.6	87.2	% 33.0	138.3	29.5	% 21.3
30	153.6	52.6	34.2	173.7	19.3	11.1
50	39.6	-31.9	-80.6	-10.2	-52.7	516.5*
65	-8.0	-57.3	719.5*	-18.7	-46.1	245.9*
75	-1.6	-49.3	3122.8*	-15.6	-60.4	388.3*
100	20.5	-32.9	-160.5	8.3	-44.5	-533.7
	Parathyroidectomized					
23	260.6	121.9	46.8	152.1	39.3	25.9
30	155.3	49.0	31.5	139.3	64.1	46.0
50	26.9	-20.7	-76.9	-2.9	-42.8	1455.4*
65	8.9	-62.7	-701.0	-20.3	-55.1	271.8*
75	2.0	-65.6	-3347.4	-17.8	-50.9	286.8*
100	20.5	-8.5	-41.3	8.3	-25.7	-308.2

\*These figures are positive, because control growth being retrogressive, gives a percentage decrement instead of increment. The quotient of this into the percentage decrement of the tests is necessarily algebraically positive in sign. The values represent the relative degree of loss of weight, notwithstanding, and are so charted.

groups strengthens the probability that the thing is real. No seasonal influence can be introduced as an explanation, since the material for each age series, as well as that for the 100 day old group, was scattered over several years of collection.

From my data, which were obtained under conditions more closely approximating the ideal than those of any previous worker, though conditions which still might be improved from

the point of view of the thymus problem, it is, therefore, evident that although there is a thymic loss of weight at puberty, this is recovered from and thymus growth continues on into the young adult period. Whether thymus growth continues throughout life

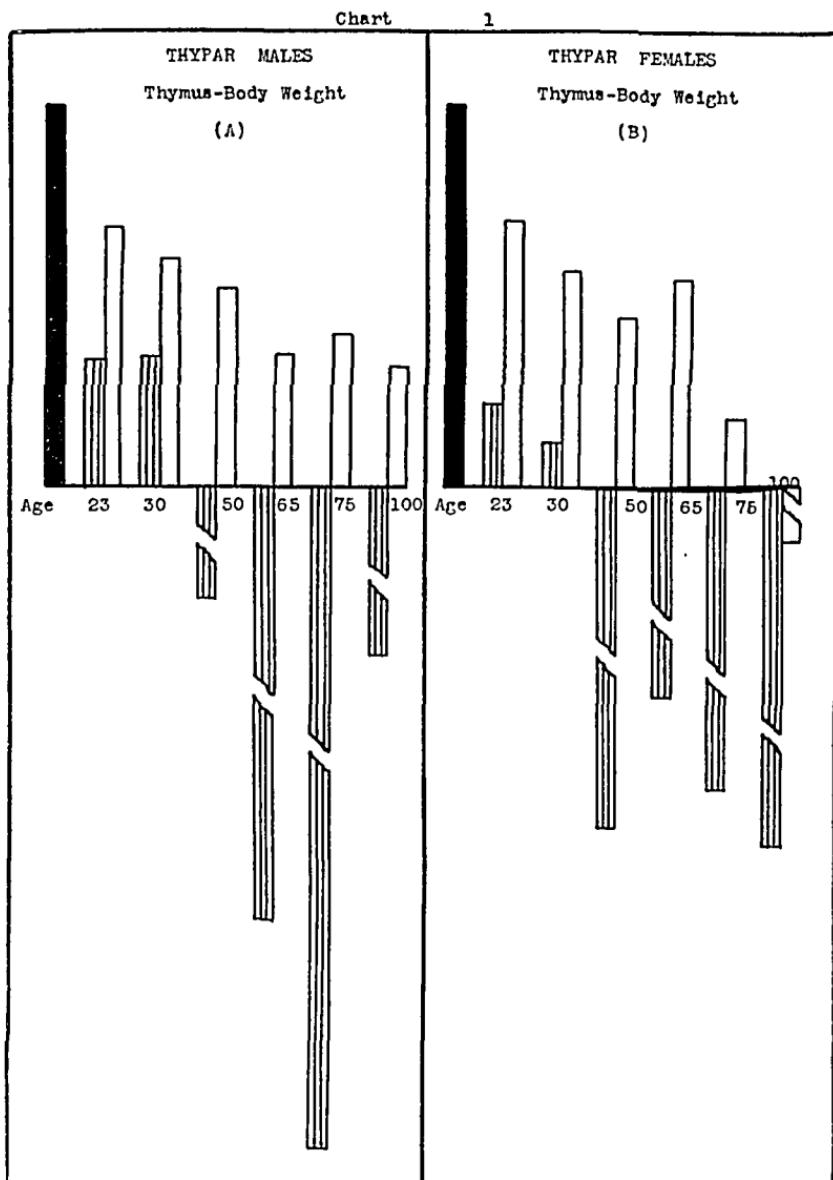


Chart 1. This chart compares the growth of the thymus with that of the body in weight after thyroid removal at the stated ages. The black column in this and every chart is control growth and is always 100 per cent. The first column of every pair is the growth of the thymus in the test animals in terms of that of the controls. The second column of every pair is the growth of the body in weight of the test animals in terms of that of the controls. Chart A gives the data for the males, while Chart B gives those for the females.

can only be determined by extending the observations under optimum conditions.

A word about recovery. It will be noted from Table 1 (control values), that the average weight of the thymus of the combined groups at 150 days of age was less than that of the reference controls at its heaviest (75 days in the male, 65 and

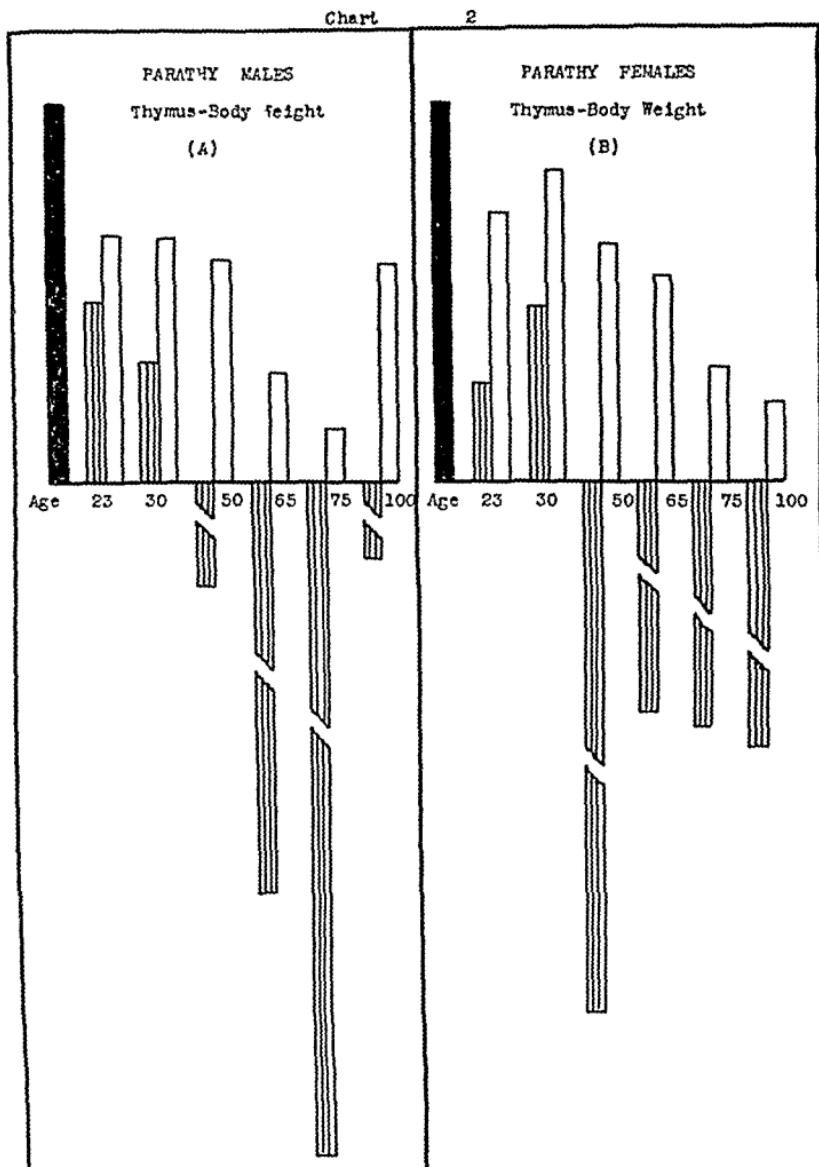


Chart 2. This chart compares the growth of the thymus with that of the body in weight after parathyroid removal at the stated ages. The first column of every pair represents thymus growth, and the second column represents body weight growth as in Chart 1. Chart A gives the data for the males, while Chart B gives those for the females.

75 days in the female), sexes being considered separately. Moreover, the mean weight of the thymus of the individual age series groups at 150 days of age was less than that of the reference controls at 65 and 75 days in the male (thyphar controls), and less than that of the female (thyphar and parathy controls) at 50, 65 and 75 days. This results in negative values

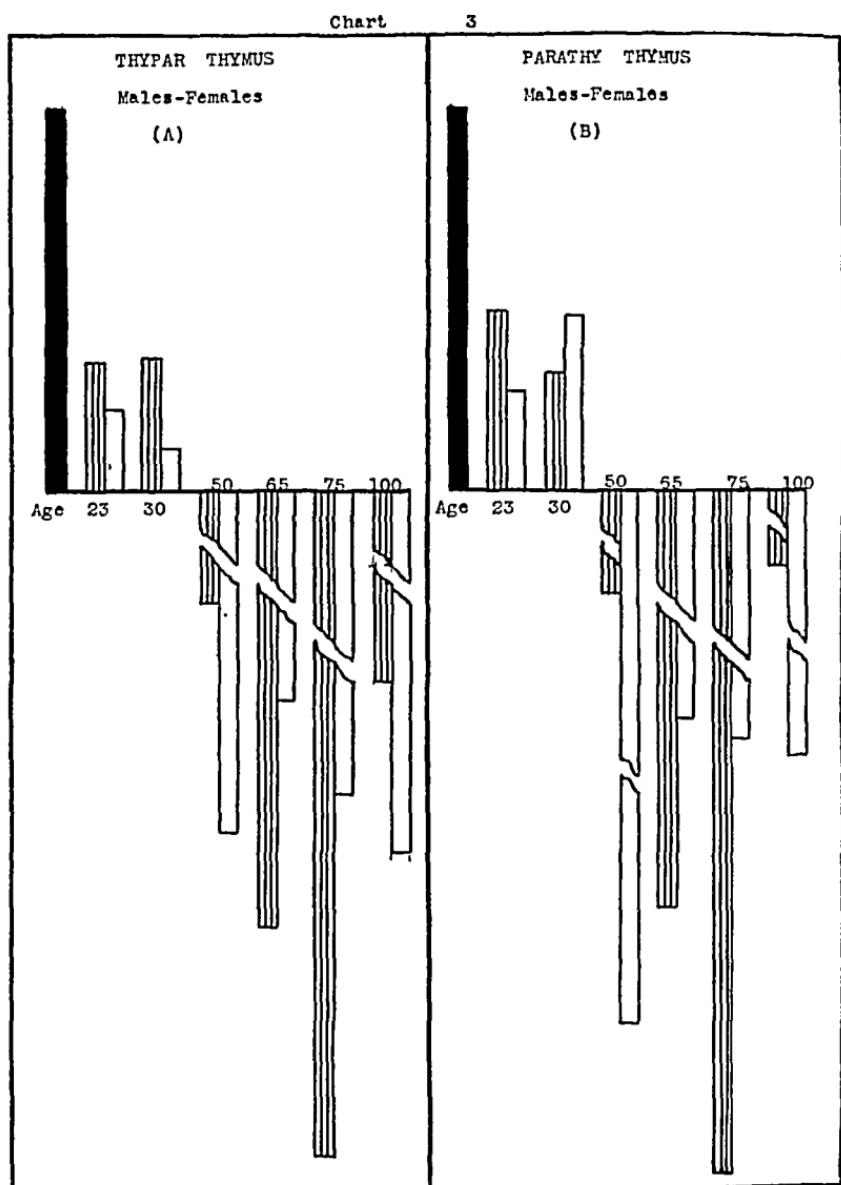


Chart 3. This chart compares the growth of the thymus in the male with that in the female after A—thyroid and B—parathyroid removal at the stated ages. The first column of every pair represents the response of the male thymus, and the second column represents that of the female.

for growth capacity (percentage rate of growth) as shown in Table 2 (control figures). It would appear as if the thymus of these series was undergoing involution during the respective intervals recorded, i. e., from 50, 65 or 75 to 150 days of age. But the mean weight of the control thymus at 150 days was greater than that at 65 and 75 days in the male parathy-

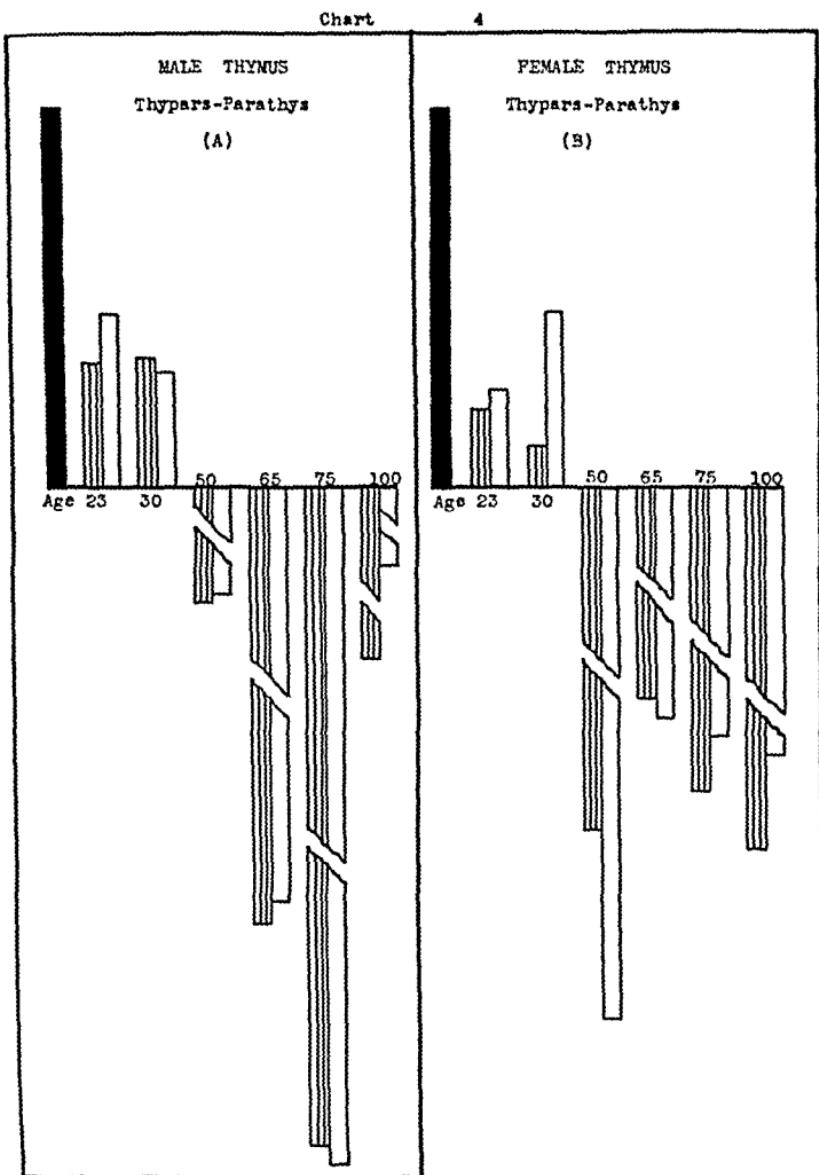


Chart 4. This chart compares the growth of the thymus after thyroid removal with that which occurs after parathyroid removal, from A—the males and B—the females. The first column of every pair represents thymus growth in the thyroidless rats, and the second column represents that in the parathyroidless rats.

controls (Table 1). Also in each of the four sets of experiments it was greater than the weight at 100 days. In addition the weight of the thymus of the 150 day old rats of the 100 day old series alone, was greater than that of the reference controls 100 days of age. As a result the growth capacity of the 100 day old series was positive as distinct from the negative or low values of the immediately preceding age series (65 and 75 days in the male thypar controls, and 50, 65 and 75 days in the female controls of both sets). It is, therefore, evident that recovery from the pubertal conditioned involution is a fact, but that its discovery depends on having record of intermediate stages between the point of greatest weight and the young adult stage. It is worthy of note that the degree of retardation of recovery as indicated by the amount of negative growth capacity is roughly directly proportional to the weight of the organ at the beginning of observation. This is seen from the following short table culled from Table 2 (control values) :

Age	Weight	G.C.
50	0.2422	— 2.9
65	0.3176	—20.3
75	0.2792	—17.8

This is probably an arithmetical rather than a physiological relation.

A similar post-pubertal recovery is observable in Hatai's figures. The mean thymus weight at 82-85 days is greater than that at 70-72 days, which in turn is less than that at 58 days. Here, however, continued growth does not occur, probably because of sub-optimal dietary or environmental conditions or disease.

The picture of normal thymus growth in the albino rat up to young adulthood, is therefore as follows: The thymus progressively increases in size up to puberty. Some time during this period a loss of weight occurs. With the completion of the pubertal adjustment growth is resumed and the organ again increases in weight. This recovery, however, does not bring the weight of the organ by 150 days of age, back to the value which was reached before the beginning of the pubertally conditioned involution. That it might do so if a longer period was provided under optimum conditions is probable.

The conclusion is that *there is no such phenomenon as the "age" involution of the thymus, at least before young adulthood long after the attainment of sexual maturity, and that puberty is not the initiator of a permanent progressive loss of weight or involution.*

Thus at least one further step is had in our knowledge of thymic growth, in that the time of onset of "developmental" involution, if such exists, is found to be beyond the puberty period, the period which Hammar has set as the beginning of the supposedly normal developmental alteration.

The question naturally arises as to whether the pubertal loss of weight is due to a direct influence of the surge in gonadal incretory activity upon the thymus, or whether it is merely a response to the general physiological disturbance incident to the particular stage of development. Since gonadal activity continues for some time after the attainment of sexual maturity it would be expected that if this is the immediate cause of the thymic recession, the latter would continue. But as the data shows, this does not happen under close to optimum conditions. Moreover, there is no specific valid correlation between gonad weight and thymus weight in the adult rat. The fifth order coefficient is  $-0.166 \pm 0.060$  in the male and  $0.061 \pm 0.055$  in the female. In view of these considerations and taking into account the known sensitivity of the thymus to adverse conditions, it seems more logical to believe that *the thymic involution of puberty is simply a reaction to the general physiological disturbance of the period.*

A critical survey of the investigations along these lines, so adequately summarized by Hammar (3), shows that each and every one of them can be interpreted on the basis of the extreme sensitivity of the thymus to sub-optimal conditions, and that no specific gonadal relationship need be postulated. That such relation is possible, I would not deny; but the evidence at present available is inadequate to demonstrate the association, and the phenomena can be interpreted on other better established grounds. Why the thymus has this high degree of sensitivity is a matter yet to be determined.

## THE EFFECT OF THYROID DEFICIENCY

For the reasons and with the limitations given elsewhere (7) the growth response to thyro-parathyroidectomy will be interpreted in terms of thyroid deficiency alone.

In Charts 1A and B the growth of the thymus is compared with that of the body in weight after thyroid removal at the stated ages. Three facts stand out.

The growth of the thymus is much more adversely affected by thyroid deficiency than is that of the body as a whole. There is no consistent parallelism between the thymus and body weight change in degree of response with change in age at time of thyroid removal. Thymic growth is recessive when thyroid deficiency is initiated at 50 days of age or thereafter.

The cause of the greater sensitivity of the thymus is unknown. The fact of its occurrence is in complete harmony with the relative reaction of thymus and body weight to nutritional defects (1) and the idea expressed in an earlier paper (7) that the growth reaction of the body to thyroid deficiency is fundamentally due to a condition of essential undernutrition.

The lack of exact parallelism of direction of response on age of the thymus and body weight may indicate that the organ is specifically different from the body in its relation to thyroid activity. The great variability of the thymus, however, makes such conclusion difficult. In the adult rat there is a fair degree of weight association between thymus and body weight. The coefficient of correlation is  $0.404 \pm 0.051$  in the male and  $0.320 \pm 0.055$  in the female (2). It would thus seem probable that this plays some part in the reaction to thyroid removal. Its expression is not clean-cut, however. It is also a question as to whether or not the reaction is due to a specific thymus-thyroid association. There is no valid weight correlation between these two organs in the adult animal either conditioned or specific. The zero order coefficient is  $0.104 \pm 0.072$  in the male and  $0.191 \pm 0.071$  in the female. The fifth order coefficient is 0.162 in the male and -0.016 in the female. On the other hand, there is a valid specific correlation between thymus and adrenals. The value in the male is  $0.187 \pm 0.057$  and in the female  $0.213 \pm 0.051$ . It may be that the adrenal retrogression plays a part in the thymus response. Interpretation, however,

is uncertain. All that can safely be said is that the thymus is extraordinarily sensitive to the total disharmony produced by thyroid deficiency and that this is accentuated by the physiological changes incident to puberty.

On Chart 3A the sex difference in thymus response is shown. The organ in the male is less sensitive than in the female save in the 65 and 75 day old series. The reversal of the relation at this time suggests a differential participation of the gonads in the total effect. But it is merely a suggestion.

#### THE EFFECT OF PARATHYROID DEFICIENCY

On Chart 2A and B the growth of the thymus is compared with that of the body after parathyroid removal at the stated ages.

As in the case of thyroidless rats, so here the thymus is more adversely affected than the body as a whole by parathyroid deficiency. There is, however, an indication of a parallelism between the thymus and body weight response direction, with respect to the change with change in age at time of glandular removal. This would indicate that the thymic reaction is largely conditioned by the general bodily condition, rather than by a specific growth relation of the organ to parathyroid activity.

Here, too, the initiation of the glandular deficiency at 50 days of age and thereafter, conditions a recession of thymus weight. Hence it is probable that the factors of puberty accentuate the sensitivity of the gland to the general disharmony.

On Chart 3B the sex difference in response is shown. Here, as in the thyroidless groups, a reversal of the sex relation occurs when the parathyroids are removed at 65 and 75 days of age. This tends to confirm the idea of a sex differential participation of the gonads in the thymic reaction. Consistent with this is the observation of Hatai (8) that the thymic hypertrophy of castration tends to be greater in degree than that resulting from spaying. Now I have shown in an earlier paper (9) that the growth of the ovary is more retarded than the testis by both thyroid and parathyroid deficiency. Hence it may be that a protective influence of a relatively more greatly diminished ovarian activity is at the basis of the lesser thymic recession in the females of the 65 and 75 day old series. On

the other hand, the thymus of the female lost more weight than did that of the male in the 100 day old series, the series in which actual atrophy of the ovaries occurred while the testes were merely retarded in growth. The facts as a whole are, therefore, not consistent with the foregoing explanation. Hence we must revert to the hypothesis that the sex reversal in the 65 and 75 day old series is merely an expression of a general sex difference in body response to the state of puberty, and that this is the immediate basis of the thymic response, rather than any specific gonadal interference. That is to say, the sex difference in thymic response to both thyroid and parathyroid deficiency initiated at these ages, is probably due to a sex difference in the general physiological condition of the organism as a whole, and not to any specific sex difference in relation to the thymus to gonad activity. This interpretation would also suffice for the sex differential reaction of the thymus to gonadectomy. I am inclined to be extremely wary of bringing in any conception of specific interglandular relationships, unless these can be based on indubitable evidence, and neither my observations nor those to be found in the literature justify any such assumption in the case at hand, when the data as a whole are critically examined. It is dangerous to postulate such conclusions when alternative explanations are available.

Support for the foregoing is had from a comparison of the relative response of the thymus to the thyroid and parathyroid deficiency, as given in Chart 4A and B.

Here it is seen that the order of magnitude of the thymic response tends to be the same in both types of glandular deficiency. Moreover, the direction of change in degree of reaction with change in age at time of glandular removal tends to be the same for each group. This similarity is consistent with the idea that the growth response to both thyroid and parathyroid deficiency is fundamentally due to the same underlying cause, namely, a reduction in the amount of materials available for growth. It is not consistent with any idea of a specific growth relation of the organ with thyroid or parathyroid function.

This absence of evidence of a specific growth relation does not, of course, constitute proof of absence of incretory interrelation. Such may or may not be present. The data merely

show that thymus growth in conditions of thyroid and parathyroid deficiency can best be interpreted on the basis of the general bodily disturbance, rather than on the assumption of a specific interglandular secretory association.

#### SUMMARY AND CONCLUSIONS

A study of thymus growth in the albino rat under close to ideal conditions with respect to diet, environment and health, shows that there is no such phenomenon as the "age involution of the thymus" up to the time of young adulthood, some time after puberty.

The thymus does lose weight during puberty, but this is temporary, and growth of the organ is resumed after the completion of the adjustment, when the animals are under suitable conditions. Hence it is evident that puberty is not necessarily the initiator of a permanent progressive loss of weight or involution of the thymus. The pubertal loss of weight is simply a reaction to the general physiological disturbance of the period, and not to any specific relation of the thymus to gonadal secretory activity.

The thymus is affected much more adversely by both thyroid and parathyroid deficiency than is the body as a whole. This is what might have been expected from the well known extreme sensitivity of the organ to dietary and other disturbances.

Thymic growth is retrogressive, i. e., weight is lost, after thyroid or parathyroid removal at 50 days or thereafter. This is to be taken as an expression of an additive effect of the normal disturbing influence of the pubertal adjustment and the total disharmony induced by the glandular deficiencies. It is not an acceleration of involution.

The distortion of thymus growth induced by thyroid and parathyroid deficiencies is best interpreted as a reaction to the general bodily disturbance. The evidence does not justify the assumption that the growth of the organ is specifically related to thyroid or parathyroid activity.

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STUDIES OF THE THYROID APPARATUS. XXXVIII.  
THE RELATIONS OF THE THYROID AND THE  
PARATHYROIDS TO THE GLANDS OF  
INTERNAL SECRETION

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INTRODUCTION

The five preceding papers of this series give a technical report and interpretation of the growth response of the glands of internal secretion as individuals [gonads (1); hypophysis (2); adrenals (3); pancreas (4); thymus (5)] to thyroid and parathyroid deficiencies initiated at 23, 30, 50, 65, 75 and 100 days of age in the post-natal life of the male and female albino rat.

Because of the similarity in the functional mode of action of these organs it seems worth while to bring the separate responses together into a summarizing paper, and to consider them as a group in an attempt to evaluate their specific and general relations to the thyroid and the parathyroid glands. The treatment of the subject in this paper will be as little technical as is consistent with clear exposition. It will be more of the nature of a generalization. The details will not be given since they may be found in the earlier reports. Recognition is had that more than one function is subserved by each of these organs, and that an incretory function of the thymus is not yet proven. The possibility is also realized that growth changes may not affect endocrine activity. Nevertheless, the assumption will be made that a growth retardation, or a loss of weight of an organ, conditions a less than normal functional output.

THYROID RELATIONS

It has long been held that the thyroid is the functional center of the incretory group. This opinion is the natural out-growth of the greater frequency of bodily disturbances traceable to thyroid mal-function as compared with those arising from other glandular derangements, and the striking clinical

manifestations of the former as compared with the more subtle sequelae of the latter.

With the discovery and isolation of thyroxin by Kendall (6) and the determination of its physiological rôle by Plummer and Boothby (7), the fact was established that a major function of the thyroid is concerned in the regulation of the metabolic rate. That is to say, the organ is a participant in the regulation of the energy exchange of the body as a whole.

The thyroid, however, is not the sole factor in this regulation, as I have pointed out in an earlier paper (8). The obviousness of this should be apparent to any one. But in view of the widespread tendency to attribute every alteration of the basal metabolism to thyroid disorder, the fact needs to be repeatedly emphasized. Otherwise it will be lost in the welter of data which is being spread upon the record.

The analysis of the course of growth in body weight subsequent to thyroid removal at different ages (8), led to the conclusion that: "The rôle of the thyroid in growth is that of a participant in the regulation of the metabolic level, through which is determined the rate of the maintenance processes of the organism and hence the amount of material presented to the cells for growth processes during a given period."

In view of this it is evident that the growth response of any particular organ of the endocrine group to thyroid deficiency is determined by the relation of its own type of metabolism to the fundamental process rate; by the reaction of its own type of metabolism to the sum total of the changes produced by the disturbance; by any specific co-ordinating relation which may exist between the function of its secretory products and those of the thyroid, and by any other inter-glandular secretory associations which may be present.

It is clear that proof of an assumed secretory interrelationship from organ size changes is no simple matter, notwithstanding the impressions to be gained from the literature to the contrary. For a lack of specific growth relation of an endocrine organ to thyroid deficiency is no proof of a lack of possible secretory association. Such, indeed, may be present; but its influence on growth masked, neutralized or destroyed by the other factors.

What the growth studies do show is the relative response of the several organs to the total disharmony produced by thyroid removal. From this an index is had of the relative change in total functional output.

These findings of biological significance bear with them certain pragmatic implications. The carrying over to man of results obtained with the rat must be done with reservation. Yet since man can not be used as an experimental animal in studies of this sort, the available material must be used if progress is to be made in extending the boundaries of knowledge for human benefit. The albino rat is undoubtedly the most satisfactory animal to use in an endeavor such as this, since its dietary habits are like those of man, and since the problem is essentially one of metabolism. Moreover, as has been pointed out in several papers from this Institute, the growth of the rat in many respects presents characteristics which are correlatable with those of man. In view of these facts no great error will be made if it is assumed, until evidence to the contrary is brought forward, that the growth changes which occur in the rat under the conditions which occur in this investigation, give an index of the response of man to like influences. Hence, for the present at least, the data can be taken by the clinician as indicating the organic changes which may be expected to occur in man under conditions of thyroid deficiency. As such they are of practical importance.

The solution of the problem as to whether or not there is any specific growth relation of the endocrines to thyroid or parathyroid deficiency can only be had, as the preceding papers show, when there is available for analysis a large number of correlatable data obtained under rigid conditions of control, and from which inter-age, inter-sex and inter-organ comparisons may be made. Isolated investigations of the growth response of single organs to these deficiencies, not only provide no means of evaluation, but also tend to lead to false conclusions.

Of assistance in interpreting the growth results in terms of possible incretory inter-relationships, and the determination of the paths along which such specifically acting associations may be exerted are the results of the biometrical analysis of the weight inter-relations of the organs in question in the normal animal (9).

It can be assumed that a specific weight association between any given pair of organs is evidence of a specific functional association, at least in the quantitative sense. On the other hand the absence of a specific weight association is no proof of the absence of specific functional correlation. Hence, negative results in this type of analysis mean nothing when taken by themselves. The studies as so far carried on indicate that the matter can not be completely clarified until accurate methods have been devised for the determination of the amount and the nature of the secretory products and of the activity of the organs producing them. Nevertheless, much suggestive material is at hand, as the following pages will show.

Now it has been found that the weight association which exists in the normal adult albino rat between the thyroid and the ovaries, pancreas and thymus is largely dependent upon the body size (10). It was also found that the growth response of each of these organs to thyroid removal (1) (3) (4) is associated with that of the body as a whole. These data are, therefore, consistent in that they show there is no specific *growth* relation between the organs in question and the thyroid. If there is any specific *secretory* relation between these glands and the thyroid, this is not a major participant in their growth.

The growth retardation which is produced is, therefore, largely conditioned by the dependency of the organs on the effectiveness of the growth processes of the body as a whole, which in turn is conditioned by their individual type metabolism and its relation to the generalized lowering of the metabolic level consequent on thyroid deficiency.

While this generalization is true, it is also true that puberty introduces another factor. This is shown by the consistent appearance of a marked change in type or degree of response (usually an increased sensitivity) of the several organs to thyroid removal at and after this period.

Now it is well known that the attainment of sexual maturity produces profound physiological and chemical changes throughout the organism. But these changes are initiated by the increment of gonadal secretory activity,—not by changes in the thyroid. Hence the change in growth response to thyroid removal ... and often ... is not so much due to

a normal shift in thyroid function as it is due to a normal developmental change in the substrate (the body and its parts) on which the function is executed. And this change in the substrate is due to gonadal secretory activity. Hence it is the gonadal secretory activity which is the conditioning factor in the change of response to thyroid removal during and after puberty.

Two paths of influence are conceivable. On the one hand it is possible that the increased sensitivity of the various organs to thyroid removal during and after puberty is simply an expression of the additive effect of the general disturbance plus the lowered metabolic level. In this case the response may be thought of as being largely conditioned by the dependence of the organs on the effectiveness of the growth processes of the body as a whole. On the other hand it is possible that certain inter-glandular secretory relations participate in the production of the end result.

Exact interpretation of the mechanism of the latter phase is impossible. Nevertheless, significant potentialities do appear to be present in some cases and the data do justify the postulation of probable influence.

Circumstantial evidence leads to the belief that there is a specific secretory association between the adult ovary and the thyroid. It is therefore probable that the increased sensitivity of the gonad to thyroid removal when and after the secretory function of the ovary is established is a result of this specific association. Which is to say that, although the growth of the ovary is largely dependent upon the effectiveness of the growth processes of the body as a whole, its regression as exhibited in the loss of weight when the thyroid is removed during and after puberty, is conditioned by a functional let-down, due to the loss of the thyroid which entails a disruption of the ovary-thyroid specific relation (1).

Now the pancreas exhibits a similar weight recession (4). This is not to be attributed to any sudden shift in relation of thyroid function to the pancreas, but rather to a change in pancreas sensitivity engendered by the increment in gonadal secretory activity.

There is no evidence from which a direct or specific gonad-

pancreas relation can be assumed. There is evidence of a specific direct weight association between pancreas and adrenals, and between gonads and adrenals in the sexually mature animal (9). There is evidence that the adrenal is the pivotal point through which the interglandular weight associations are correlated (10). Now the adrenals undergo a weight regression when the thyroid is removed during and after puberty. It is, therefore, possible that the gonad change determines the adrenal loss of weight, which in turn participates in determining the increase in pancreatic sensitivity to thyroid deficiency. That is to say, the adrenals are probably a connecting link between the gonads and the pancreas in the observed reaction to pubertal and post-pubertal thyroid removal. The data as a whole are also consistent with the idea expressed in an earlier paper (9) that the adrenals are the functional center of the endocrine system of the sexually mature animal.

In the case of the thymus it is impossible to dig out from the data any kind of specific or direct incretory basis for the increased sensitivity of the organ to thyroid removal during and after puberty (5). One of the characteristics of the organ which differentiates it from the others is its exquisite sensitivity to changes in general body conditions. This sensitivity is expressed in a loss of weight or atrophy. The general organic disturbances incident to puberty produces such a loss of weight in the normal animal, from which recovery may be had if optimum conditions are provided. No sure evidence is had, however, that the pubertal reaction is due to a specific gonad-thymus relation. The reaction is interpretable just as logically on the basis of the natural sensitivity of the organ to a general bodily disturbance such as puberty is known to bring out. The only conclusion that is at present justified is that the increased sensitivity of the thymus is due to the summation of its normal reaction to the general bodily disturbance initiated by gonadal incretory activity and the general disharmony produced by thyroid deficiency. These two combined result in sub-optimal conditions of such degree that growth is impossible. This, then, as can readily be seen, is non-specific, and justifies the classification of the thymic reaction to thyroid deficiency as essentially

due to its dependence on the reaction of the body as a whole. It is not an acceleration of involution.

From the observations of Jaffe (11), that the adrenals play some as yet undetermined part in thymus involution, it might be inferred that this relation participates in the thymic reaction to pubertal and post-pubertal thyroid removal. Particularly in view of the fact that there is a specific weight association between the gonads and adrenals in the sexually mature animal. But the facts are not consistent with the assumption. In the first place thymic regression follows thyroid removal at 50 days of age, but no marked shift in adrenal growth reaction occurs in these same animals. In the second place, Jaffe found that thymic involution is *retarded* when the adrenals are removed (adrenal deficiency), while in my experiments the thymus loses weight when the adrenals lose weight (and presumably diminish in total functional output) under conditions of thyroid deficiency. This inconsistency of thymic reaction prevents the introduction of an adrenal factor in the interpretation. True, it may be that such is present, but its influence is quite overbalanced by the general disorganization incident to the lack of thyroid function.

The testis is another organ the growth of which is not specifically related to thyroid activity (1). It differs from the three glands (ovary, pancreas and thymus) just discussed in that it is singularly resistant to the growth-retarding influence of thyroid deficiency initiated before the pubertal adjustment. It also differs distinctly from the body as a whole, up to this time, both in degree and type of change in response with change in age at time of thyroid removal. The greater resistance is due to the fact that the normal type of growth of the testis provides a substrate which is peculiarly different from that of the rest of the body. This is because the testis is an organ the growth of which up to puberty is more largely represented by growth by increase in cell number than is that of the body as a whole or its other parts. Now, since this growth by increase in cell numbers is less susceptible to retardation by thyroid deficiency than is growth by increase in cell mass (8), it is obvious that the organ possessing it in relatively greater proportion should be more resistant to the disturbance than the

body as a whole or the other organs which possess a lesser proportionate representation of total growth in this form. That is to say, the individuality exhibited by the testicular reaction to thyroid deficiency initiated before the completion of the pubertal adjustment, is not an expression of an inherent specificity of relation to the thyroid, but is rather an expression of a specificity of growth type resistance to the changes in effectiveness of the growth processes of the body as a whole. That this point of view is correct is shown by the fact that with the completion of pubertal developmental growth, the reaction of the testis to thyroid deficiency approximates that of the body as a whole, both in degree and in type.

The testis is like the three glands already discussed, in that the pubertal adjustment brings about an increase in sensitivity to thyroid deficiency. But neither the expression nor the basis is the same. The testis undergoes no loss of weight or retrogression when the thyroid is removed during or after puberty. Moreover, evidence that specific incretory factors are of influence is lacking. The phenomenon is explicable on the basis of the normal developmental shift from a growth type where a large proportion of the total growth (expressed as gain in weight) is growth by increase in cell number, to a type where the proportion is more like that of the body as a whole. The result of this is that the testis follows the body weight in the response to thyroid removal. The conclusion, then, is that the growth independence of the testis to thyroid deficiency initiated prior to the completion of the functional developmental phase of growth of the organ is due to its high rate of growth by increase in cell number, a phase of growth relatively resistant to thyroid deficiency; and that the growth reaction to thyroid deficiency initiated after the functional developmental phase is largely determined by the dependence of the organ on the effectiveness of the growth processes of the body as a whole.

It is not to be denied that the increment in testicular incretory activity of puberty may participate in the reproduction of the end result. But all the evidence points to the idea that this is exerted through the reaction of the body as a whole, and not through any specific gonad-thyroid incretory relation.

Turning now to the adrenals, it has been found (3) that the growth of these organs after thyroid removal prior to puberty,

parallels that of the body in weight. It is, therefore, clear that the effectiveness of the growth processes of the body as a whole is the major factor in determining the growth response to thyroid deficiency initiated during this pre-pubertal phase of development. The changes which are brought about in the body as a whole by the increment in gonadal secretory activity also affect the adrenal substrate. Evidence is also had that thyroid secretory activity is a participating factor in adrenal growth. This evidence is the fact that there is a specific adrenal thyroid weight association in the adult albino rat of both sexes (9), and the fact that the previously existing parallelism between adrenal and body weight response to thyroid deficiency is disrupted when the thyroid is removed during and after puberty. The proof of the injection of the gonadal secretory factor is had from the increase in sensitivity (or growth regression) which follows thyroid removal at 65, 75, and 100 days of age. That this is the major factor in the increased sensitivity has already been shown in previous paragraphs. That it is not necessarily the true factor concerned in the disruption of the adrenal-body weight parallelism of response is shown by the fact that, whereas an increased sensitivity of adrenal reaction occurs when the parathyroids are removed at these same ages, the parallelism of the adrenal-body weight response is generally maintained.

Hence the evidence of a specific pubertal and post-pubertal participation of thyroid secretory activity in adrenal growth is indisputable. It may indeed be true that such a relation is effective before the pubertal adjustment, but if this is so, its influence is marked by the greater influence of the response of the growth processes of the body as a whole.

Since it is only when the pubertal adjustment has brought about the change in the adrenal substrate that proof of specific thyroid participation appears, it is just to conclude that the secretory relationship of the gonads to the adrenals is a major factor in determining the response of the latter to thyroid deficiency.

The gonads, pancreas, thymus, and adrenals possess three features in common with respect to their growth response to thyroid deficiency. The first is that they show no specific growth

relation to thyroid deficiency initiated before puberty. Their response is generally interpretable on the basis of the effectiveness of the growth processes of the body as a whole. The second is that no influence of inter-glandular incretory relation as affecting growth is evident when the thyroid is removed before puberty. And the third is that the increment of gonadal incretory activity which comes on at puberty determines in all an increased sensitivity to thyroid deficiency, which is usually, though not always, expressed by a loss instead of a gain in weight.

To sum up, it is apparent that in addition to being subjected to the growth-disturbing effects of the lowered metabolic level, the response of the organs to thyroid removal during and after puberty is conditioned by new influences. These are: a possible specific or direct gonadal incretory influence; the general bodily disturbance and change brought about by the increment of gonadal incretory activity; the possible inter-mediation of a specific gonad-thyroid incretory association; and the incretory co-ordination of the adrenals. It is quite possible that all of these factors are participants in the reaction. On the other hand, the data seems to justify the opinion that their relative influence differs with the different organs. Which of course is what is to be expected on the basis of inherent organ differences in metabolic activity and function.

Turning now to the hypophysis, we have an organ which is distinctly different from the others in that it is quite clearly specifically affected by thyroid deficiency (2). Its growth response to thyroid lack does not parallel that of the body as a whole. No evidence is had that the increment of gonadal incretory activity in the male has any influence whatsoever. In the female, on the other hand, while a gonadal incretory influence is evident, it does not produce the same type of reaction (recession) as in the other organs.

A further sex difference is present in that the gland does not undergo hypertrophy in the female save when the thyroid is removed at the height of puberty (65 days of age). These sex differences are consistent with the fact that there is a specific gonad-hypophysis weight association in the adult female, but not in the male (10). From this it is clear that a sex dif-

ference in gonadal secretory function (or perhaps a sex difference in organic constitutional functional make-up) is the contributing factor to the sex difference in hypophyseal response. It is also clear that the hypophysis in the female is subject to ovarian secretory influence. This brings up the question of sex specificity in secretory alignment, a matter of great practical as well as biological interest. This phase of the problem, however, must be left for another paper.

Coming back to our main thesis, viz., the difference between the reaction of the hypophysis and that of the other organs to thyroid deficiency, no hint is had in the male of the participation of any other secretory activity. This is consistent with the fact that the hypophysis in this sex exhibits no specific weight association with any of the other glands of internal secretion, save the pancreas. It may be that this relation participates in the hypophysis reaction to thyroid deficiency, but if so it is masked by the specific influence of the thyroid in producing the hypophyseal hypertrophy.

Of the five organs being reviewed in this paper, two only show convincing evidence of specific growth or weight relation to thyroid deficiency. These two, the adrenals and the hypophysis, are also the only two which are almost exclusively endocrine in function. This, therefore, brings up the idea that if it were possible to measure the constituents of endocrine function in the pancreas, gonads and thymus (*sic*), it might also be found that this part of these organs is also specifically related to the thyroid, and that it is the growth reaction of the organ as a whole which masks or prevents the expression of the relation of the part.

Emphasis should be given to the fact that these suppositional associations, as well as those already established have been found to be, are probably conditioned if not determined by the stage of development of the organism, particularly that stage which is concerned in the development of sexual maturity with its increment of gonadal secretory activity.

If a growth comparison of the several organs under conditions of thyroid deficiency is made, it is found that the order of decreasing growth capacity is pretty generally: hypophysis, gonads, adrenals, pancreas, thymus. This holds for both sexes and all ages, with three exceptions.

A reciprocal shift in position of the adrenals and pancreas occurs in the thyroidless males of the 65 and 100-day-old series. In the females of the 100-day-old series the ovary goes from the second to the fourth position, all the other organs retaining their respective places.

Although no conclusion can be made as to the causes of these misalignments, certain data suggest possible bases for ultimate interpretation.

The pancreas in the adult male is somewhat specifically correlated with the hypophysis, thymus and adrenals in weight (10). It is, therefore, possible that the changes induced in these organs by thyroid deficiency are participating factors in those of the pancreas. On the other hand, the adrenals are specifically correlated with the thyroid and to a greater degree than with the pancreas, while the pancreas shows no specific weight association with the thyroid at all. Hence, it is possible that the shift is initiated by the adrenals rather than by the pancreas.

In the case of the ovary it may indeed be that the marked increase in relative sensitivity lies in the fact that the body itself lost weight in this group (the 100-day old series). For it is well known that the ovary is more liable to undergo a greater loss of weight in conditions of under-nutrition, than are any of the other organs of this series, save the thymus.

However that may be, the fact remains that the differential response is remarkably uniform in character, notwithstanding the great changes in the intensity or degree of individual reaction.

Certain implications are derivable from this uniformity.

Now it is obvious that each separate organ is characterized by the possession of a specific type of functional metabolism which is superimposed on or interrelated with the general type common to all living cells of the body. It is this specific type which not only sets the organ apart as a functional entity distinct from the others, but which also participates in the determination of the characteristic growth rate, under abnormal as well as under normal conditions.

The uniformity noted above, therefore, indicates that the disharmony induced by thyroid deficiency reaches and maintains a state of equilibrium, so that the individual growth or organ

size reaction also reaches and maintains its characteristic relation to that of the others regardless of developmental changes or differences in sex factors of influence. That is to say, systemic qualitative relations are independent of developmental or sex differential factors.

This ability of the thyroidless rat to equilibrate its growth relations has already been pointed out in an earlier paper (8).

The way in which each individual organ maintains its position in relation to the others regardless of developmental and sex differential factors, shows that the relation of the individual organ to the effectiveness of the growth processes of the body as a whole, is the prime factor in the determination of the relative growth response to thyroid deficiency, and that specific relations to the thyroid (save in the case of the hypophysis), or to the other incretory forces are not effective factors of immediate influence. That is to say, it is not the specific functional relation of any particular organ of this group to any other, but it is the specific relation of the individual organ to the sum total of the conditions produced in the body as a whole, which determines its relative reaction to thyroid deficiency.

These data justify a reiteration of the general principle that the organism must be considered as a functionally interlocking whole, and not as an aggregate of discrete and separately functioning parts.

#### PARATHYROID RELATIONS

The symptomatology of parathyroid deficiency has given rise to the belief that the parathyroids protect the organism from developing a neuro-toxic state. The mechanism through which this protective function is executed has yet to be established. Whether it is through a regulation of the calcium exchange; whether it is through a prevention of the formation or accumulation of some neuro-toxic substances analogous to the guanidines, or whether the two processes are combined, are problems still to be solved.

Since the present studies deal with the rôle of the parathyroids in growth, it is not the place to go into a discussion of the conflicting data concerned with the causation of tetania parathyreopriva. All that is sufficient and necessary here is to determine whether the evidence justifies the conclusion that a

function of the parathyroids is directly or specifically concerned in growth and development.

The analysis of the course of growth of the body as a whole subsequent to parathyroid removal at different ages (8) led to the conclusion that: "The parathyroids are not concerned in growth except in so far as they protect the organism from the growth retarding influences exerted by toxic products resulting from parathyroid deficiency. The retardation of growth which obtains is largely attributable to a lowering of the nutrient level following a disturbance in effectiveness of the digestive system due to the response of the sympathetic system to the toxemia."

In essence, the growth of the body as a whole is not specifically related to parathyroid activity.

The growth response to parathyroid deficiency, of any particular organ of the group being studied may be determined by the relation of its own type of metabolism to the lowered nutritional level; by the reaction of its own type of metabolism to the sum total of the changes produced by the disturbance; by any specific co-ordinating relation which may exist between its secretory functions and those of the parathyroids; by any other inter-glandular secretory associations which may be present, or by combinations of these several factors.

It has been found that the growth of the gonads (1), hypophysis (2), adrenals (3), pancreas (4), and thymus (5) is not specifically related to parathyroid activity. If there is any specific secretory relation between these glands and the parathyroids, it is not an evident participant in their growth.

The growth retardation which does occur in conditions of parathyroid deficiency, is largely conditioned by the relation or dependency of the organs on the effectiveness of the growth processes of the body as a whole. That is to say, by the sum total of the changes produced by the glandular removal. This is shown by the fact that the growth of the organs in general parallels that of the body weight in its response to parathyroid removal at the different ages.

Since this finding is like that derived from the study of the organ response to thyroid deficiency, it is additional support for the belief that the basic cause of the growth disturbance is the same in both types of glandular deficiency, viz., a condition of essential undernutrition.

The introduction of gonadal incretory activity which takes place at puberty is a secondary factor conditioning the reaction of the several glands to parathyroid deficiency. As pointed out earlier, this influence may be exerted through the change it produces in the body as a whole, or it may be exerted through specific inter-glandular incretory associations.

The response of the pancreas (4) and the thymus (5) to parathyroid deficiency initiated when this stimulus is in force is apparently determined by the general body response and not by any specific relation of the organs to gonadal activity. The same is true in the case of the hypophysis (2) of the male. In the female, on the other hand, evidence is given that the pubertal surge in ovarian incretory activity has a specific influence on hypophyseal response. This sex difference is consistent with the fact that there is a specific gonad-hypophysis weight association in the adult female, but not in the male (10).

The growth of the testis is highly resistant to the lowering of the nutritional level brought about by parathyroid removal. The organ thus exhibits the same specific type of reaction to thyroid and parathyroid deficiency. The basis of the specificity is the same in the one case as the other, *i. e.*, a greater relative resistance of growth by increase in cell number to metabolic disturbances of this type, combined with a greater relative proportion of total growth being represented in the testis by growth by increase in cell number, than is present in the body as a whole or its other parts. The partial identity of relationships is at one and the same time an explanation and a proof of the justness of the interpretation, as well as of the belief that the growth disturbances following thyroid and parathyroid removal are based on a common underlying condition (8), viz., a condition of essential under-nutrition.

Notwithstanding this specificity, the pubertal surge in gonadal incretory activity conditions an increased growth retardation of the organ in parathyroid removal. This is quite like that experienced by the body in weight. Hence it is probable that the new stimulus acts through its effect on the body as a whole in determining the response to the glandular deficiency, rather than in any specific way. In this respect, then, the testis is quite like the hypophysis, pancreas and thymus.

Body size factors are the apparent determining cause of ovarian growth retardation in conditions of parathyroid deficiency initiated at any stage of development prior to the completion of the pubertal adjustment, *i. e.*, 100 days of age. Parathyroid removal at this time is followed by a loss of weight or atrophy of the ovary, notwithstanding the fact that body growth continues. This is indication that the sexually mature ovary is quite sensitive to conditions brought about by parathyroid deficiency, and a hint that the relation is specific. It is only a hint, however, and conclusion must be held in abeyance.

The adrenals also, in the female, show no evidence of specificity of reaction until parathyroid removal at 100 days. Their growth response to the deficiency initiated prior to this time is largely determined by the relation to the sum total of the body changes. The interruption of the parallelism, which is expressed by a loss of weight, is probably due to a direct influence exerted by the incretory functions of the ovary. This conclusion is based on the fact that there is a specific positive adrenal-ovary weight correlation in the adult female (9). Although the path of action is not determinable at present, the evidence favors the idea that the initiating agent for the increased sensitivity to the parathyroid deficiency arises in ovarian incretory function, rather than from adrenals, or from any specific relations of the adrenals to parathyroid function at this time.

In the male, the increment of gonadal incretory activity brings about a marked increase in sensitivity of the adrenals to parathyroid deficiency which is expressed as a loss of weight. This is also consistent with the fact that the testis is specifically and positively correlated in weight with the adrenals.

From this brief description it is seen that direct influence of gonadal incretory function on the reaction to parathyroid deficiency can be postulated in several cases. The mode and path by which this influence is exerted is, however, unknown. It is also unknown whether such influence is acting in the case of the pancreas, thymus and hypophysis of the male, and masked by the greater intensity of relation of the organ to the response of the body as a whole, or whether there is an organo- and sex-specific distinction. For the sake of simplicity, if for nothing else, I am inclined for the present to favor the former conception.

To sum up:

The major factor determining the growth response of the glands of internal secretion to parathyroid deficiency is the relation of the growth of the individual organ to the effectiveness of the growth processes of the body as a whole. A secondary factor of importance is introduced with the increment of gonadal secretory activity which takes place at puberty. This new addition to the endocrine complex seems to exert a direct and specific influence on the response of the ovary and hypophysis of the female, and the adrenals of both sexes, to the general conditions brought about by parathyroid removal, though it does not displace their dependence on the body processes as a whole. In the case of the pancreas, thymus, testis, and hypophysis of the male, the gonadal secretory influence is not made manifest as a direct-acting factor, but as a factor which specifically affects the growth effectiveness of the body as a whole, and through this indirectly the growth reactions of the organs named.

A study of the differential response of the several organs shows that there is no such uniformity of directional difference in degree of response as is exhibited when the thyroid is removed. The inconsistency cannot be traced to the age of the animal at the time of glandular removal. It is also sex indifferent.

Since it is indubitable that a basic cause of growth retardation is the same in each type of glandular deficiency, *e. g.*, a condition of essential under-nutrition, it would, *a priori*, be expected that the relative growth response of the several organs would show the same uniformity in the one group as in the other. Hence the chaos in parathyroidectomized rats as compared with the consistency of relative response in the thyroidless groups is apparently out of line with the principle underlying my interpretation. This straw-man is easily disposed of, however.

The study of the course of growth in body weight after parathyroidectomy led to the conclusion that there is an alternate accumulation and disposal of growth-retarding products in these animals (8). Therefore, since each organ has its individual rate of growth, which is dependent not only on the effectiveness of the growth processes of the body as a whole, but also on its own characteristic functional type, it is obvious that the growth relation of a given organ would not necessarily bear the same time relation to a given cycle as that of another organ. One would

respond less rapidly than the other to the increase and decrease in development of the growth-retarding conditions. It is also possible that the different series would be at different stages in the cycle at the stated age at which they were all killed (150 days) and the organs removed and weighed. Hence the size or condition of an organ in one series would not be expected to be in the same relative position with regard to another, as in a different series, at any given moment, such as the termination of the period of observation.

In the case of thyroid deficiency conditions are quite different, for here there is merely a steady and consistent lowering of the metabolic rate, and no evidence of alternate accumulation and disposal of toxic products acting indirectly to retard growth.

The group response of the organs to parathyroid deficiency is further differentiated from that caused by thyroid removal by the fact that the growth retardation caused by the former is generally less than that brought about by the latter. This indicates that the lowering of the metabolic rate by thyroid removal produces a greater inadequacy of materials available for growth, than does the lowering of the nutritional level which occurs on parathyroid removal.

The same difference in response to the two types of glandular deficiency is exhibited by the body as a whole. This, combined with the fact that the parallelism of organ growth response with that of body weight is closer in the case of the parathyroidless than in the case of the thyroidless groups, is further support, if any is needed, for the conclusion that the major factor in the growth reaction of the group is, in both cases, the relation to the effectiveness of the growth processes of the body as a whole.

It can be postulated as a general biological principle that individual organ differences in growth reaction to a common disturbance type, are accentuated and brought into greater relief, the greater the underlying cause of the disturbance is distorted away from the norm. Hence the lesser parallelism between organ and body-weight growth response to thyroid removal is probably due to the greater reduction in the materials available for growth, which is brought about by the lowering of the metabolic level.

While it is possible that differences in thyroid and parathyroid incretory participation, in a specific instead of a general regulatory sense, may be participants in the production of the differences in organ and body-weight group parallelism, no evidence is available in support of the idea. In the light of present knowledge, therefore, the phenomenon is more logically explained as in the preceding paragraph.

#### SUMMARY AND CONCLUSIONS

This paper presents a correlative review of the growth response of the endocrine group of organs (hypophysis, gonads, adrenals, pancreas and thymus) to thyroid and parathyroid deficiency initiated at different stages of development in the post-natal life of the albino rat of both sexes.

The evidence available justifies the belief that the incretory activity of the parathyroids is not specifically concerned in the growth or development of any of the other glands of internal secretion. The major factor in the production of the growth retardation of these organs, is the close relation of their growth processes to those of the body as a whole. These latter are reduced in expression because of the virtual lowering of the nutritional level resulting from parathyroid removal.

In the case of the thyroid the evidence points to the conclusion that there is a specific incretory association between this organ and the hypophysis, adrenals during and after puberty, and the ovary, in the adult animal. It is probable that this association participates in the determination of the growth reaction to thyroid removal. No such specificity of relation is exhibited by the testis, pancreas and thymus of both sexes, and the adrenals before puberty. Hence the growth of these organs is apparently not specifically related to thyroid function.

The principal factor of influence in all cases save the hypophysis is, however, the relation of the growth processes of the individual organ to the effectiveness of the general growth processes of the body. The reduction which is caused in the latter by the lowering of the metabolic rate consequent on thyroid removal, is the essential basis of the growth retardation observed.

The increment of gonadal incretory activity which takes place at puberty is a secondary factor conditioning the reaction

of the several organs to both thyroid and parathyroid deficiency. Evidence is had that this influence may be exerted either directly, or indirectly through the production of a general bodily disturbance. The details are to be found in the text.

The several organs exhibit a uniformity of growth-retardation relationship after thyroid removal which is pretty consistently independent of the age or stage of development at which the thyroid is removed, and which is sex-indifferent. The order of the series, on the basis of decreasing growth capacity, is: hypophysis,—gonads,—adrenals,—pancreas,—thymus.

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## CONGENITAL SYPHILIS AND GIANTISM\*

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The following case is of interest because of the association of congenital syphilis and unusual development of the bony skeleton. The immediate cause for hospitalization was advanced pulmonary tuberculosis.

### CASE REPORT

J. W., aged 21, single, born in the United States.

**Family History:** Paternal grandfather and grandmother were under 5 feet 8 inches in height and all siblings were short. Father was 6 feet 2 inches tall, and died of tuberculosis. Information regarding maternal grandparents was unobtainable. Mother was 5 feet 10 inches tall. She was very queer, passing close friends and even relatives without speaking, and refusing to admit callers to her home. She was always a mystery to her relatives, who believed her expansive ideas about great wealth, although there was no evidence of such. She died with what was termed "necrosis of the roof of the mouth," which "ate away her nose and mouth." One maternal aunt died suddenly with "throat trouble." One maternal uncle had throat trouble and throughout life talked with a thick nasal voice. Two other uncles were known to have had throat trouble of a vague nature, one of whom is supposed to have died from it, and the cause of death in the other was unknown.

**Siblings:** There were no known miscarriages, and definite syphilis in the family was unknown, but the information regarding this point was inadequate and indefinite. One child died at the age of 2 years of "summer complaint," and was known to have had convulsions throughout its life. The second child died at the age of eight months of "spinal meningitis."

**Past History:** The patient had scarlet fever when a child, influenza at the age of 20 which was followed by tonsillectomy. He had some ulcer-like lesions on his legs when a small child. There was no history of convulsions or central nervous system disease.

He was obliged to attend an ungraded school and even then experienced difficulty in making satisfactory progress. He was always readily managed; he worked and played well with other children. It was found that he could do forms of manual labor in which no special intellectual requirement was necessary. He had worked for about two years as a press feeder in a print shop at twenty dollars a week.

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*Present Illness:* Three weeks before admission to the hospital the patient had been exposed to inclement weather and caught cold. He developed a sore throat and a few days later a pain in his right chest. This shifted to his left chest and persisted. There was a sharp, knife-like pain on inspiration. He felt feverish and chilly.

*Physical Examination:* The patient was a markedly emaciated young adult, moderately anemic, who appeared chronically ill, and coughed occasionally. He was 76½ inches (194.3 cm.) tall, weighed 132 pounds (60 kg.), arm span 76 inches. Temperature ranged slightly above normal.

*Head:* Patient had a triangular shaped face with prominent frontal bossae; there was a slight asymmetry of the face about the nose.

*Eyes:* Pupils were equal, round, but reacted sluggishly through a restricted arc; there was a noticeable exophthalmos.

The nose and ears and sinuses were normal.

*Mouth:* The teeth were very irregularly formed and in poor alignment. The upper incisors showed a white line and lateral incisors were hypoplastic, tending to be peg-shaped. The central incisors were typically notched (Hutchinson's). The palate was very high and narrow; tongue slightly coated; tonsils small.

*Neck:* There was a small group of submaxillary and posterior lymph nodes, enlarged on the left side. The thyroid was palpable but not enlarged.

*Chest:* The chest was symmetrical and normally developed, but markedly emaciated. There were numerous fine moist rales in the apices of both lungs, more numerous on the right side. There was slight dullness to percussion on both sides. Breath and voice sounds were distant over both upper lobes.

*Heart:* The cardiac area was not enlarged; there was a short hazy loud systolic and a snappy diastolic sound. The aortic sound was extenuated; there were no murmurs, and the rate was regular and not rapid.

*Blood Vessels:* All palpable vessels were noticeably thickened but compressible.

*Abdomen* normal.

*Genitals* normal. Normal distribution of pubic hair.

*Extremities:* Normal except for emaciation, and there were many small ulcer scars on both shins. The spine showed a slight kyphosis. There was a very marked exaggeration of the carrying angle of the elbows, and the upper third of the tibiae were markedly roughened. The hands were excessively large and he wore a number 12 shoe.

*Neurological Examination:* Ophthalmoscopic examination was negative; the pupils were equal, round, and reacted sluggishly through a restricted arc; they reacted slightly to convergence, and the consensual reflex was present. There was no nystagmus. There was a

slight facial asymmetry, an asymmetrical pharynx, a nasal lisping speech. He was slightly deaf in both ears. The superficial reflexes (corneal, pharyngeal, abdominal and cremasteric) were all present and approximately normal. The deep reflexes were greatly increased and there were bilateral ankle and knee clonus. No gross sensory changes were noted. The gait was unsteady and he showed a general weakness, probably from emaciation.

*Mental Examination:* The patient had no obvious perceptual difficulties, but had a low intellectual status. He finished seven grades in school, failing in two. He placed the capital of New York as Washington, located Pennsylvania as "some place out in New Jersey," and was unable to name any other states than New York. He failed to recognize the names of Massachusetts or Canada. He made many mistakes in simple arithmetic, being unable to correctly multiply 8 times 8, or subtract 50 minus 20, or 15 minus 7, to give the answer to  $\frac{1}{2}$  of 10, and numerous similar tests. His thought content was childish and his judgment undeveloped. There had been no disposition change, and his emotional trend was unusually happy and optimistic, with an even stable temperament. He had shown no misconduct. He was interested in his surroundings and sociable with his fellow patients.

*Laboratory Data:* White blood cells, 8,400, neutrophiles 60%, small lymphocytes 28%, large lymphocytes 2%, large mononuclears 8%, eosinophiles 2%. The urine on two examinations was normal. The serum Wassermann was negative. The spinal fluid was clear and under normal pressure. There were eight cells (lymphocytes) per cubic millimeter and a normal reduction of Benedict's solution. The globulin tests were negative; the Wassermann was negative, and the colloidal gold read 0000000000.

*X-Ray Examination:* The skull showed a type of osteoporosis, a stigma which we have found often in undoubted cases of congenital syphilis and which we are inclined to believe is due to the syphilis (18). The sella turcica was normal in size, shape and position. The tibiae showed no changes. The roentgenogram of the chest showed tuberculosis of both apices with cavity formation in the right.

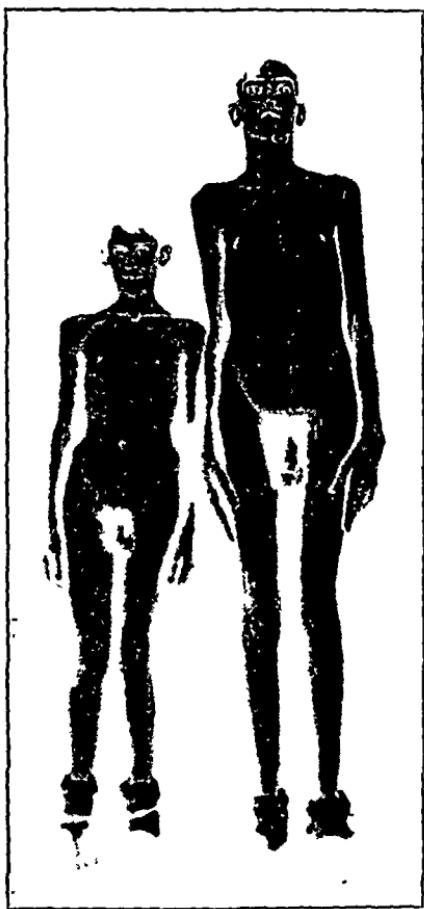
*Diagnosis:* Latent systemic congenital syphilis, with generalized skeletal overgrowth and pulmonary tuberculosis.

#### DISCUSSION

The diagnosis of congenital syphilis in this case was made despite the negative serum Wassermann, and normal spinal fluid. It is based on the general history and the many somatic stigmata, osteoporosis of the skull, prominent frontal bossae, pupillary reactions, slight facial asymmetry, high arched palate, Hutchinson's teeth and other dental anomalies, increased carry

ing angle of the elbows, roughening of the upper third of the tibiae, tibial scars, and thickening of the palpable arteries. The feeble-mindedness may or may not be related to the congenital syphilis, but the writer is inclined to associate it with it.

The diagnosis of congenital syphilis in the presence of the negative Wassermann reaction may be questioned, but there is much opinion supporting the view that congenital syphilis may be present in the adult without a positive Wassermann reaction,



Left—Lorrain type of infantilism. Height 5 ft. 2 in.  
Right—Present case of giantism. Height 6 ft. 4½ in.  
Both are approximately the same age.

definitely expressed by Leredde (16), Du Bois (6), Stoll (25), Higoumenakis (11), and others. Whether such cases are regarded as having no active syphilis or as the damaged goods of a systemic maternal toxin is a question around which much

debate has arisen. The majority of such cases will show definite progress when given antiluetic therapy. The spinal fluid in this case was also normal, the Wassermann and colloidal gold being negative. It is generally recognized that the spinal fluid in congenital syphilis may be normal even in the presence of gross central nervous system damage [von Gudfeld and Meyer (27), Solomon (24), Bounhoure (3), and Tezner (26)].

The association of congenital syphilis with tuberculosis is frequently reported, and many excellent papers have been written discussing the relationship between these two [Lereboullet (15), Munro (20), Hollander and Narr (12), etc.]. The consensus seems to be that syphilis is a predisposing factor to a subsequent infection of tuberculosis, but any direct relationship has not been proven.

The literature in the field of skeletal overgrowth connected with congenital syphilis is rather scant.

E. Fournier (7) discusses the disturbances of growth, including giantism as well as dwarfism, in his Paris thesis of 1898, which unfortunately the writer has not been able to obtain. It is discussed, however, by Bassoe (2), Barthelemy (1), and Hutinel (14), and Castex and Waldorp (5). He includes in his thesis a case reported by Buhl among instances of giantism associated with congenital syphilis. The case is summarized in detail by Bassoe, who states that for no very clear reason it was regarded by Fournier as a case of congenital syphilis. It was probably included, as suggested by Castex and Waldorp (5), because of the extensive hyperostosis of the skull, a stigma recognized by Fournier as syphilitic.

Sirena (23) presents the case of a male, 240 cm. high, weighing 213 kg., of normal parents. He died at the age of 20 from nephritis. Postmortem examination showed an overdevelopment of the skeleton, synostosis of the skull sutures, single breast bone, osteoporosis of the girdle bones and extremities, and tremendous increase in size of all the viscera. He believed that the process started very early in childhood, and the changes were clearly luetic.

Nobl (21) reports the case of a 26-year-old male showing many luetic signs in which there was an excessive skeletal de-

velopment, hypertrophic osteoarthropathy, and extreme albuminuria. He believed the condition dependent upon syphilis.

Fuchs (8) reports a male, 26 years old, whose mother had had six abortions, and one of whose brothers died at the age of one year of syphilis. The patient was 188 cm. tall and weighed 88 kg. He presented enlarged lymphnodes, slightly undeveloped genitalia, one arm larger than the other, and a nephritis which was helped by antiluetic therapy.

Wieting (29) reports an 18-year-old giant of 215 cm. (or if the kyphoscoliosis and knee deformity shortening were added, 225 cm.) without marked disproportionate body, except the scapulae. There was a local hyperplasia of the distal bones of the arm, tibia and femur, deformity of the vertebral column by kyphoscoliosis, and genu valgum. The mother of the patient was definitely luetic.

Pel (22) reports a case of a 16-year-old male with acromegaly and infantilism who also had an infantilistic sister. The testicles appeared to be normal but the penis was little developed. The patient was 197 cm. tall, but weighed only 72.5 kg. There were no definite stigmata of syphilis although the father had contracted syphilis two years previous to his marriage, and the mother had had five abortions. Pel regards the probable cause as congenital syphilis.

Levi and Franchini (17) describe a case of an acromegalic giant, a male 66 years old, 199 cm. tall, who gave a positive Wassermann test, Argyll Robertson pupils, slight optic atrophy and other signs of tabes. Bassoe, in reviewing the case, states he probably had hereditary syphilis.

Gazzolo (9) reports a case of a 28-year-old patient with generalized acromegalic features. Hereditary syphilis was regarded as the causal factor because of positive Wassermann reaction, pigmented scars on the shins, slightly unequal pupils, and amelioration following mercurial treatment. The skull was not radiographed.

Marriott (19) reported a case of a male 19 years of age with extremely long feet and hands. A roentgenogram of his skull showed a small sella turcica which was regarded as indicative of pituitary insufficiency. Infantilism also was present. The Wassermann test was positive and after vigorous syphilitic treatment the secondary sexual characteristics developed, the

pituitary body became enlarged and the patient became much more alert mentally.

Hutinel (14) is conservative regarding his opinion as to the role of congenital syphilis in giantism, but suggests that it may be the cause of the changes in the genital glands or even in the thyroid which occasionally result in giantism. He quotes the thesis of E. Fournier, Delphy, and R. Barthelemy (1). Such a case is reported by Werther (28), who reports the case of a 16-year-old male with unusually long lower extremities whose genitals were the size of a boy of 6 years.

In their extensive work on the endocrinopathies associated with congenital syphilis, Castex and Waldorp (5), under the discussion of the pituitary, briefly mention giantism. They present a case of a male of 26 years of age, with many signs of congenital syphilis, and a positive Wassermann test, who is described as being of unusually large stature "with a tendency to giantism." The actual height is not given.

In the present case presented, in view of the fact that the genitalia were apparently normal and a roentgenogram of the skull failed to show changes in the sella turcica, it is speculative whether the skeletal overgrowth may be regarded as gonadal or pituitary in origin. Regarding his sexual development, the patient stated that he had never had coitus but said he frequently had erections and occasionally had desire for it. There was some evidence of acromegaly, particularly noticeable in large hands and feet. During the period since puberty, continued oversecretion of the pituitary had changed the picture from simple giantism to early acromegalic giantism. The question as to whether the patient was primarily a youthful giant or a case of acromegaly makes little difference, if we agree with Brissaud and Miege (4), and Hutchinson (13), since it is generally regarded that when acromegaly is associated with giantism the latter always appears first.

The case is unusual in that it presents the association of skeletal overgrowth with congenital syphilis. Because of the fact that so many of the stigmata characteristic of congenital syphilis were present, it may be the cause of the growth disturbance, particularly in view of the numerous references in the literature to congenital syphilis and the endocrinopathies.

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# CLINICAL SYMPTOMATIC HYPEREPINEPHRINISM

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Evans' demonstration that the prolonged administration in rats of a potent extract obtained from the anterior lobe of the hypophysis produces a condition of acromegaly established what was long believed clinically, that this disease is caused by excess secretion of the anterior lobe of the hypophysis. Of the numerous clinical "hyper" syndromes this is the only one which up to the present time has been proved by unequivocal experimental evidence.

Whether exophthalmic goiter is actually caused by thyroid hypersecretion still remains to be proved. Although it is true that it has not been possible to produce the symptom-complex in animals by feeding thyroid, nevertheless, many clinicians, with a certain amount of justification, as will be pointed out presently, consider the disease clinically as "hyperthyroidism." Their justification lies in: (1) Thyroid overgrowth is an almost constant accompaniment of the disease.\* (2) The outstanding pharmacologic action of thyroxin is to increase heat production. Increased heat production, moreover, is one of the most constant clinical findings in active exophthalmic goiter. This is further supported by the fact that thyroidectomy lowers heat production and that a subnormal respiratory exchange is characteristic of thyroid insufficiency.

On the basis of the known pharmacologic actions of epinephrin a clinical syndrome is herein depicted which may be described as "Clinical Symptomatic Hyperepinephrinism." The outstanding pharmacologic actions of this internal secretion are first, its pressor, and second, its metabolic effects.

The influence of epinephrin upon blood pressure is well known and needs only to be referred to briefly. Following its

\*The histologic changes in the thyroid in exophthalmic goiter have been very much over emphasized and given undue significance. It has been clearly demonstrated, especially since the frequent administration of iodine in exophthalmic goiter, that they are both of varying constancy and not specific. Suffice it to point out that there is no necessary relationship between the clinical manifestations of the disease and the histological picture in the thyroid in Graves' disease.

injection into the body this substance causes a marked rise in arterial blood pressure which lasts usually about five minutes and then commences to fall. If the excess of epinephrin be constantly introduced this pressor effect would be maintained, thus giving rise to clinical hypertension, assuming the heart is sufficient.

Injection of epinephrin into the body also increases the respiratory exchange causing an augmentation both in the oxygen intake and the carbon dioxide output. This was observed in 1912 by Fuchs and Roth (1) and has been confirmed by a host of workers, including Bernstien (2), Tompkins, Sturgis and Wearn (3), Sandiford (4), Lusk (5), Marine and Lenhart (6), and others. Marine and Lenhart (6) and also Sandiford (4), demonstrated further that this increase in the respiratory exchange occurred even after thyroidectomy. These results show that it may act independently of the thyroid. This is of importance for in the syndrome herein to be described goiter is absent, indicating that the excess of epinephrin, assuming that it does occur, acts without influencing the thyroid.

There are several other changes which injection of epinephrin may give rise to. It first accelerates the heart by primary stimulation of the accelerator nerves to this organ. This is followed by a short period during which the heart beat is slowed as a result of secondary stimulation of the vagus center, which soon relinquishes its control to the more powerful accelerator stimulation so that tachycardia finally persists.

The increased pulse rates seen in our clinical cases may, assuming our hypothesis is correct, have their origins in a phenomenon akin to that just described, or they may be mere accompaniments of augmented heat production.

Epinephrin may cause increased glycogenolysis, giving rise in some instances to glycosuria. This symptom has been at times observed in several of our cases. As a result of this, in one patient a diagnosis of diabetes mellitus of mild nature has been made (7) (8).

#### CHARACTERISTIC FEATURES OF THE SYNDROME

The outstanding signs of the syndrome are:

- (1) Increased basal metabolic rate (hyperthermia).

- (2) Hypertension (systolic and diastolic).
- (3) Tachycardia.
- (4) Loss in body weight.
- (5) Nervousness.
- (6) Pigmentation of the skin.

All of our eight cases were between the ages of 33 and 56. Six were women. All of the patients presented a fairly typical picture. They were thin and appeared nervous and restless, as if suffering from some discomfort. The skin was warm, and darkly pigmented. There was not the pronounced hyperhidrosis so constantly seen in cases of exophthalmic goiter with equally as high metabolic rates. Goiter was either absent or only of slight degree, and in all instances lacked the pulsation, bruit, vascularity and softness, which occurs so commonly in exophthalmic goiter before involution (by iodine) takes place. Tachycardia was present in each case. The fine tremor of the fingers and marked asthenia, almost constant accompaniments of Graves' disease, were not seen in our group of cases. True hypertension, both systolic and diastolic, and its consequent cardiac hypertrophy were present in every case. The respiratory exchange studied under basal conditions was likewise definitely elevated in each instance.

#### DIFFERENTIAL DIAGNOSIS

The outstanding condition from which these cases must be differentiated is exophthalmic goiter. Indeed Read (9) has already expressed the belief that these may be cases of exophthalmic goiter with merely a coincidental hypertension.

The characteristic blood pressure findings, however, in exophthalmic goiter, contrary to what was observed in our group, are systolic hypertension with normal or low diastolic pressure, giving rise to a high pulse pressure. This is in keeping with the dilated peripheral vascular tree which is characteristic of this disease. Moreover, such important stigmata of exophthalmic goiter as exophthalmos, thyroid overgrowth, fine tremor of the fingers, asthenia, and gastro-intestinal crises, are conspicuous by their absence in the cases which we are here classifying separately.

Another important point is the fact that iodine did not

influence the heat production in those patients of our group to whom it was administered. This is a biological test for active Graves' disease and its result is of much significance in a differential diagnosis of this nature.

Too much emphasis cannot be placed also upon the fact that three of our cases were subjected to subtotal thyroidectomy (in one patient thrice in four years), without relief and with persistence of both the elevated heat production and hypertension. Roentgen ray treatments when used were likewise ineffective.

The progress of the cases which we have observed is of significance also in differentiating this condition from Graves' disease. Most patients with the latter ailment pass through periods of remissions during which they feel improved and eventually in many instances the disease actually undergoes spontaneous arrest. The prognosis, at all events, is usually good, both as to control of symptoms as well as life. In our group of cases with hypertension and elevated metabolism, which we believe should be classified separately, the course of the disease has usually been progressive, three having already succumbed.

The question of the influence of cardiac disease or hypertension *per se* upon the basal metabolic rate has been made the subject of another communication by the author. I studied the respiratory exchange in more than 40 such cases and found all of their metabolic rates to be within the accepted normal limits provided the test was performed under basal conditions (10).

There are, up to the present time, eight cases in our series. Seven have already been published (7) (8). A brief description of the eighth case, which I recently encountered in private practice, follows:

Mrs. S., a housewife, aged 36 (referred by Dr. Herman Schwatt), commenced to suffer from throbbing headaches about eight years ago. At about the same time she became nervous and noticeably lost weight. Although goiter was not present, she was given several courses of x-ray treatments to the thyroid area over a period of  $2\frac{1}{2}$  years, but with no relief. She was told at that time that she also had high blood pressure. Her family history is unimportant. Menstruation commenced at 12, and has always been regular. Occasionally there is slight dysmenorrhea. She was pregnant once but miscarried at three months. Her chief complaints at present are: headaches, loss in weight, nervousness, palpitation of the heart and sharp pains in the calves of her legs when walking, necessitating frequent rests.

The patient is poorly nourished, her weight is 50 Kg. (110 lbs.) and her skin is warm to the touch, although not unusually moist. There is no exophthalmos. The thyroid is not palpable. No pulsations nor bruit are present over it. There is marked pulsation of the neck vessels and concentric cardiac enlargement. A systolic murmur can be heard over the apex and over the aortic orifice. The aortic second sound is accentuated and the aortic arch is widened. The pulse rate is 96 and regular. The lungs are clear and resonant throughout. The abdomen is negative except for the forcible aortic pulsations which can readily be felt through the thin abdominal wall. There is no tremor of the fingers. The muscle strength is fair. The knee-jerks are slightly exaggerated. The pulsations of the dorsalis pedis arteries are readily felt and both these and the radials do not feel unduly thickened. The blood pressure is 210/110. A basal metabolic rate done three years ago was plus 28% (Benedict apparatus). In June, 1926, it was plus 25% and R. Q. .77. The urine (single specimens) showed constantly low specific gravity, 1006 and 1008, acid in reaction, no sugar, faint trace of albumin, rare granular casts, and few white blood cells. In June, 1926, the blood sugar was 128 mg. and urea 12.6 mg. per 100 cc. blood. The blood Wasserman reaction was negative.

#### SUMMARY OF EIGHT CASES CONSTITUTING GROUP

Case No.	Age Sex	Blood Pressure		Basal Metabolic Rate	Pulse Rate	Remarks
		Sys.	Diast.			
1	45 F	240	135	+84%	140	Pigmentation of skin. No exophthalmos. No goiter.
2	42 F	260	175	+45%	96	Chronic glomerulonephritis. Pigmentation of skin. No goiter. No exophthalmos. Patient died.
3	37 M	180	110	+34%	90	Symptoms for over seven years. Subtotal thyroidectomy thrice.
4	50 F	220	110	+38%	110	Died of cerebral hemorrhage.
5	33 F	160	95	+56%	124	Röntgen ray treatments. Subtotal thyroidectomy. No exophthalmos.
6	55 M	275	180	+30%	80	Erys of jaw. Died of cardiac insufficiency.
7	56 F	210 260	90 110	+38%	120	Thyroid adenoma for over 30 years. Mild diabetes mellitus, hemiplegia.
8	36 F	210	110	+25%	96	No exophthalmos. No goiter. Röntgen ray treatments.

#### SUMMARY

A syndrome is described, the outstanding symptoms of which are increased basal metabolic rate and vascular hypertension (systolic and diastolic). If an excess of epinephrin is artificially introduced into the body the pharmacological effects

are such that there results these same abnormal changes, namely, augmentation of heat production and elevation of the blood pressure. Upon this basis it is therefore suggested that in these cases there is operating a condition of excessive epinephrin action and the syndrome is described as "Clinical Symptomatic Hyperepinephrinism." It appears to act independently of the thyroid.

The points of differentiation between this symptom-complex and exophthalmic goiter are enumerated and described.

An additional illustrative case is recorded. .

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## Abstract Department

Comparative experiments on the action of l- and d-adrenine on the gas exchange of organs in different conditions (Vergleichende Versuche über die Wirkung von l- und d-Adrenalin auf den Gaswechsel von Organen in verschiedenem Zustande). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, 212, 523-534.

Both in intact and in minced striped muscle no difference could be detected in the action of l- and d-adrenine on the gas-exchange. A concentration of 1:50000 was necessary to produce an increase of oxygen consumption. Both l- and d-adrenine produced increased oxygen consumption in stomach and heart muscle, the former more. Minced stomach muscle is relatively insensitive to adrenine. Liver tissue, intact or minced, is affected similarly, and more favorably by l-adrenine.—A. T. C.

Effect of adrenalin upon blood sugar following ligation of the hepatic artery. Collens (W. S.), Shelling (D. H.) & Byron (C. S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 545-546.

"Ligation of the hepatic artery causes an abnormally high degree of carbohydrate oxidation with a total depletion of glycogen stores of the body." During this process adrenalin 1/1000 intravenously injected has less and less effect the longer after ligation it is injected. When hypoglycemia has developed, adrenalin does not affect the blood sugar level. When adrenalin does not influence the blood sugar level, the glycogen in the tissues is becoming exhausted and hypoglycemic convulsions will occur in a few hours.

—J. C. D.

Total metabolism and the adrenals (Le metabolisme de sommet et les capsules surrénales). Giaja (J.) & Chahovitch (X.), Compt. rend. Acad. d. Sc. (Par.), 1925, 181, 885-886.

Adrenalectomized rats cannot alter their thermogenesis, which cannot be raised above the basal value. The injection of adrenine permits an increase of total metabolism, sometimes to the height of the normal rat.—A. T. C.

Adrenal secretion produced by asphyxia. Houssay (B. A.) & Molinelli (E. A.), Am. J. Physiol. (Balt.), 1926, 76, 538-549.

The effect of asphyxia on adrenal discharge was studied in dogs. It was found that closure of the trachea produced a marked

adrenal discharge in 2 to 5 minutes, reaching the maximal point in 5 to 6 minutes. It can be as much as 0.045 mgm. per minute. This discharge was registered by a recipient dog showing, a, rise of blood pressure; b, increased heart rate; c, constriction of the denervated limb. Respiratory paralysis produced by curare or cobra venom produces asphyxia and consequently adrenal discharge. Potassium cyanide produces adrenal discharge. Diminished oxygen tension is the efficient cause of the discharge in these cases. CO<sub>2</sub> accumulation has no apparent effect. Asphyxia acts on the central nervous system and the stimulus is transmitted through the splanchnics.—Authors' Summary.

**Functioning autoplastic suprarenal transplants.** Jaffe (H. L.) & Plavská (Alexandra), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 528-530.

The adrenals were removed from rats, cut in two and the parts retransplanted between the fascia and abdominal wall. The medulla degenerates in most cases and the cortex remains and increases in size. Out of 67 rats only 6% died instead of 40% which is the usual death rate after adrenalectomy.

In guinea pigs the same procedure was followed except that the medullary tissue was removed, and the cortical material cut into small pieces for transplantation. Out of 19 cases 5 died within 4 days, as is usual after adrenalectomy in this animal. The other 14 lived more than two weeks and six were still alive and growing at the end of three months.—J. C. D.

**Animal experiments on the physiological metabolic action of certain hormones. I. The action of adrenine in starvation (Tier-experimentelle Untersuchungen über die stoffwechselphysiologische Wirkung bestimmter Hormone. I. Die Wirkung des Adrenalin im Hungerzustande).** Junkersdorf (P.) & Török (P.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 414-432.

Adrenine produces in starved animals a marked hyperglycaemia on the first day, which gives place to normal values on the second, and in most cases recurs on the third day. In some animals in which starvation was continued after cessation of adrenine definite hypoglycaemic values were obtained. The amount of adrenine used is within limits apparently without influence on the initial time of action, or the height or duration of the hyperglycaemia.

Usually there is a parallel glycosuria. Blood and urine nitrogen were usually increased in the adrenine period, water content of the blood lowered, diuresis increased. The liver was practically glycogen-free, and its weight was extraordinarily low 72 hours after the last adrenine dose. Definite fat-infiltration of the liver occurred. Muscle-glycogen was less than in starved controls.

—A. T. C.

Central stimulation of the adrenals and the abdominal chromaphil body during insulin poisoning (Ueber die zentrale Reizung der Nebennieren und der Paraganglien während der Insulinvergiftung). Kahn (R. H.), Arch. f. d. ges. Physiol. (Berl.), 1926, 212, 54-63.

Poll's results, that following insulin-poisoning in the mouse there result morphological changes in both parts of the adrenals, are confirmed for rabbits and dogs. In dogs the change affects the abdominal chromaphil body also. The morphological changes of the chromaphil tissue are accompanied by diminution of its adrenine content. Section of the splanchnic in rabbits protects the adrenal medulla from this insulin action.—A. T. C.

Epinephrin reaction in obesity. Krantz (C. I.) & Means (J. H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 698-699.

The rise in metabolism and change in ventilation after epinephrin was the same in the normal and the obese. There was a smaller rise in the respiratory quotient and in pulse pressure in the obese as compared to the normal.—J. C. D.

Clinical action of adrenalin upon premature contractions. Otto (H. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 814-815.

Twelve patients with different types of heart disease showing premature contractions were selected. These received 1 c.c. of a 1 to 1000 solution of epinephrin hypodermically. The electrocardiogram showed that the number of premature contractions was increased.—J. C. D.

The prenatal growth and natal involution of the human suprarenal gland. Scammon (R. E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 809-811.

The uterus undergoes a period of rapid increase in size just before neonatal involution. An analysis of 1087 cases was used to determine whether there was a similar acceleration in growth in the adrenal just before the involution which takes place at birth. Figures and a chart are given to show that this is not the case.

—J. C. D.

The endocrine basis of pernicious vomiting in pregnancy. Dickson (W.), Practitioner (Lond.), 1926, 116, 365-374.

The author argues that the vomiting of pregnancy is due to glycogen starvation in the tissues. This is the result of the overactivity of the islet tissue of the pancreas and a lack of balance between the output of adrenin and pituitary hormone. The author uses mammary substance to counteract this condition.—J. C. D.

**A hormone of heart-movement. IV. Experiments with alcoholic heart extracts (Ueber ein Hormon der Herzbewegung. IV. Versuche mit alkoholischen Froschherzextrakten).** Haberlandt (L.), Arch. f. d. ges. Physiol. (Berl.), 1926, **212**, 587-600.

The alcoholic extract is active, and withstands boiling. The "heart-hormone" is therefore not a protein. The ether extract is inactive, so that this hormone is not a lipoid.—A. T. C.

**The hormone and nervous regulation of fat metabolism (Das hormonal-nervöse Regulationssystem des Fettstoffwechsels).** Raab (W.), Ztsch. f. d. ges. exper. Med. (Berl.), 1926, **49**, 179-269.

A report of investigations, together with an extensive review of the literature and full discussion to which the reader is referred for details. Starvation of dogs regularly increases blood fat and ketone bodies. This increase is not particularly influenced by subcutaneous injection of extracts of thyroid, gonads or pineal. Insulin does not influence blood fat but decreases ketone body content of blood for many hours with subsequent marked increase which can be prevented by glucose ingestion. Antuitrin in most cases was without effect on blood fat, but in a small number of instances acted like a small dose of pituitrin, which fact the author assigns to contamination by the latter substance; antuitrin affects ketones like a small dose of pituitrin. Pituitrin subcutaneously decreases blood fat and ketones to a marked degree. Smaller doses injected into the lateral ventricles give an intense reaction. This reaction fails completely or is greatly retarded after injury of the infundibulum and tuber cinereum, after section of the cord, after splanchnic section on one side or after phosphorus poisoning. The pituitrin reaction is restarted by adrenalin and insulin. Adrenalin alone decreases blood fat in fewer cases than does pituitrin; after nervous lesions the adrenalin effect is irregular. Ingestion of glucose by starving dogs decreases blood fat even after midbrain lesion; it is effective for ketones only in large amounts. The author thinks there is no direct relation between blood fat and blood sugar. After cord section, as well as after administration of adrenalin following injury to the tuber cinereum, there is a marked percentage increase in dry substance of blood, while in most experiments the reverse occurs.—C. I. Reed.

**On the relation of certain endocrines to the salt content of rat blood.** Rohdenberg (G. L.) & Krehbiel (O. F.), J. Cancer Research (Lancaster), 1925, **9**, 422-424.

Hypermineralization of the blood of rats was found to occur to the extent of 35% as a result of an incised wound; 45% after splenectomy; and 67% after thymectomy. In each case there were "about the same changes in the relative amounts of potassium,

calcium and sodium." Thyroideectomy increased the total salts in the blood by 110%, with a 13% increase in sodium and a similar decrease in potassium. Castration caused a hypermineralization of 177%, with an increase of 18% in the sodium content. Adrenalectomy caused the greatest increase of 203%, with the very low calcium content of 9.5%.—J. P. S.

**Hermaphroditismus externus feminus.** Bell (W. B.), Am. J. Obst. & Gyn. (St. Louis), 1925, 10, 778-789.

True hermaphroditismus externus feminus is rare, and is probably a result of a sudden access of masculinity-producing secretions after the genitalia have almost completely developed in foetal life. The individuals should always be regarded as females. The treatment recommended is the excision of the phallus and the exposure and enlargement of the entrance to the vagina.—M. O. Lee.

**Histological studies of the right genital gland of the ovariectomized hen** (*Études histologique de la glande génitale droite de la Poule ovariôtomisée en un testicule*). Benoit (J.), Compt. rend. Acad. d. sc. (Par.), 1926, 182, 240-243.

Total precocious extirpation of the left ovary of the hen results in the transformation of the right genital gland into a testis, whose development can proceed up to the elaboration of spermatozoids. Histological studies confirm this conclusion.—A. T. C.

**An investigation into the causation of the onset of labor by parabiosis during pregnancy.** Kross (I.), Am. J. Obst. & Gyn. (St. Louis), 1926, 11, 64-69.

Eleven pairs of pregnant rats, in different stages of gestation, were united in parabiosis, with common abdominal cavities. In 8 pairs each animal went into labor at the usual time at the termination of its own period of gestation. The animal less advanced in pregnancy continued to the end of its normal gestation period without being affected by the labor of its twin.—M. O. Lee.

#### **Experimental hermaphrodisim and antagonism of the sex glands.**

**VI. The significance of operative interference on the testis for the condition of female hormonal effects** (*Experimenteller Hermaphroditismus und der Antagonismus der Geschlechtsdrüsen.* VI. *Ueber die Bedeutung des operativen Eingriffs am Testikel für das Zustandekommen des weiblichen hormonalen Effekts*). Lipschütz (A.) & Voss (H. E. V.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 266-278.

After one-sided castration the remaining intact testis does not prevent normal development of a transplanted ovary but inhibits the consequences of such transplantation, fewer positive results appearing than after complete castration.—A. T. C.

**Experimental hermaphroditism and antagonism of the sex glands.**

VII. Disturbance of spermatogenesis and the female hormonal effect (Experimenteller Hermaphroditismus und der Antagonismus der Geschlechtsdrüsen. VII. Störung der Spermatogenese und weiblicher hormonaler Effekt). Lipschütz (A.), Tiitso (M.), Suvikul (D.) & Vesnjakov (S.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 279-304.

When the testes are transplanted into the abdomen without damaging their blood supply, intrarenal ovarian transplantation produces female hormonal effects within a few weeks. Experimental cryptorchism, essentially disturbance of spermatogenesis, results.—A. T. C.

**Experimental hermaphroditism and antagonism of the sex glands.**

VIII. The significance of spermatogenous substance for the production of female hormonal effects—hormone and substrate (Experimenteller Hermaphroditismus und der Antagonismus der Geschlechtsdrüsen. VIII. Ueber die Bedeutung spermatogener Substanzen für das Zustandekommen des weiblichen hormonalen Effekts—Hormon und Substrat). Lipschütz (A.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 305-323.

It is thought that the disturbance of spermatogenesis resulting from the inhibitory effect of the female hormone on the testes is produced through sensitizing substances produced autolytically in the canals of the testis from the sperm-producing cells and not of hormonal nature.—A. T. C.

**Experimental hermaphroditism and antagonism of the sex glands.**

IX. The law of constant follicle number. Influence on ovarian transplants through the ovaries *in situ* (Experimenteller Hermaphroditismus und der Antagonismus der Geschlechtsdrüsen. IX. Das Gesetz der konstanten Follikelzahl. Die Beeinflussung des ovariellen Transplantats durch die Ovarien *in situ*). Lipschütz (A.), Adamberg (L.), Tiitso (M.) & Vesnjakov (S.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 682-696.

The follicular development of intrarenal ovarian transplants was inhibited by the presence of ovaries *in situ*, although they remained in 4 or 8 female guinea pigs for 7 months. Only in one case was a large Graafian follicle present, and in none were corpora utea present in the transplant. This lends new support to the law of constant follicles.—A. T. C.

**Experimental hermaphroditism and the antagonism of the sex glands. X. The different sex-reaction on the ovarian transplant. Comparative experiments with ovarian transplants in males and females (Experimenteller Hermaphroditismus und der Antago-**

nismus der Geschlechtsdrüsen. X. Die geschlechtsverschiedene Reaktion auf das ovarische Transplantat. Vergleichende Versuche mit Overientransplantation bei Männchen und Weibchen). Lipschütz (A.), Tiiro (M.), Voss (H. E. V.), Vesnjakov (S.) & Adamberg (L.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 697-721.

Marked differences are observed with ovarian transplants into castrates of the two sexes. Males show a stormy progressive development within 2 or 3 weeks, which can lead to milk secretion within 6 weeks. In females there is an intensive development, interrupted by more or less regular pauses, to some extent corresponding to the oestrus cycle and seldom proceeding as far as in the male.—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. XI. Hyperfeminisation and protracted rut (Experimenteller Hermaphroditismus und der Antagonismus der Geschlechtsdrüsen. XI. Hyperfeminierung und protrahierte Brunst). Lipschütz (A.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 722-744.

The ovarian transplant shows a sex difference in itself, shown by histological differences, when implanted into castrated males and females. The stormy development of the mammary apparatus in castrated males infers a protracted rut.—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. XII. Influence of age of the host on the carrying out of the female hormonal effects. Conclusion (Experimenteller Hermaphroditismus und der Antagonismus der Geschlechtsdrüsen. XII. Der Einfluss des Alters des Wirtstieres auf das Zustandekommen des weiblichen hormonalen Effekts. Schlusswort). Lipschütz (A.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 745-760.

An immature ovary transplanted into an adult male develops to maximum endocrine action in 2 or 3 weeks, but transplanted into a young male develops only after about 6 weeks. The same period is required for an adult ovary transplanted into a young male. The endocrine action depends therefore on the age of the host and not of the ovary.

Histologic interrelationships of menstruation and ovulation. Novak (E.), Am. J. Obst. & Gyn. (St. Louis), 1925, 10, 802-807.

A review of recent work in this field. Most workers agree that ovulation occurs at a variable time after menstruation, but most usually at about the 13th or 14th day of the cycle. Ovulation is believed to be a necessary precursor of menstruation.

—M. O. Lee.

The relation of thymus and testes to growth. Paton (D. N.), Edin. M. J., 1926, New Series 33, 351-356.

Observations testes of 185 children between 2 and 17 years old show that there is an acceleration of testicular growth at the age of 15. This corresponds with the beginning of thymic involution as shown by Hammar's work. The author discusses the work of Halmar and Marshall (1914) on guinea pigs showing that their results can be interpreted to indicate (1) an increased growth of the testes following thymectomy, (2) a retardation of growth under 300 grams, after combined thymectomy and castration.

—J. C. D.

Therapeutic use of ovarian graft. Pettinari (V.), Gynécologie et Obstétrique (Par.), 1926, 13, 19; Abst. J. Am. M. Ass., 86, 1731.

Pettinari applied ovary grafting in 332 animals, dogs, rabbits, rats, etc. The grafts survived only in animals of the same species and with a manifest deficiency of the sex hormone. The results were negative in cases of old ovariotomy, or after removal of the uterus. An early grafting seemed to prevent the by-effects of ovariotomy. It also stimulated the mental activity and functioning of different organs in old animals. The experimental findings afford a sound basis for ovary grafting in women. The clinical indications for it are: defective or arrested development of the sex organs; removal of ovaries and pathologic menopause; sterility of ovarian origin; syndromes from endocrine glands, also certain mental affections. Further research may prove the efficiency of ovarian grafts in senility. The purpose of the grafting may be stimulation of the ovarian gland or substitution of its function. The grafts may be implanted in the genital organs or close to them, intraperitoneally or extraperitoneally. Good results were obtained with implants in Douglas' pouch or in front of the bladder. It is possible that the retrorenal space may be advantageously used for implantation of the ovary.

Studies on the physiology of reproduction on birds. Riddle (O.) & Reinhart (W. H.), Am. J. Physiol. (Balt.), 1926, 76, 660-675.

The relation of the parathyroids to reproduction has been studied by means of measures of the serum calcium of male and female pigeons kept under constant conditions of food and confinement. Data were obtained for thirteen different stages of the reproductive cycle. A role of the parathyroids in avian reproduction has been found and described. Male doves and pigeons show no marked fluctuations of the serum calcium level in the various stages of the cycle. Female pigeons regularly show an extremely large increase in blood calcium—to double the normal value—at each ovulation period. This rise of blood calcium in the female

begins approximately 123 hours before the beginning of the formation of an egg-shell, and is no wise explained by a large calcium "need" for shell formation. It is probably first of all an expression of a newly found relation which the parathyroids bear to reproduction in the female bird. During three to five days female pigeons withstand, without trace of adverse effect, a degree of hypercalcemia considerably in excess of that thought by Collip and co-workers to result in death in dogs. The available evidence for blood calcium changes during menstruation, pregnancy, lactation and menopause in the human and other mammals is discussed. Evidence for a seasonal change in the level of blood calcium is found. In immature pigeons lower values were found in winter and higher values in summer. In this same animal it is known that the testes and ovaries undergo a size change in the same direction as the serum calcium, and that the thyroid is largest at the time the serum calcium is at its minimal seasonal value. Insufficient and inconclusive data were obtained on the question of a sex difference in the amount of calcium in the blood. These studies were made in continuation of an extended examination of the mechanisms by which forced or crowded ovulation effect modifications of sexuality and sex ratios in pigeons. It is found that under the conditions which bring about those sexual changes the parathyroid activity, as measured by the serum calcium, is maintained at an abnormally high level.—Authors' Summary.

**Simplified method of preparation of ovarian hormone and properties of purified product.** Ralls (J. O.), Jordan (C. N.) & Doisy (E. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 592-593.

Detailed instructions for purifying the hormone are given. Chemical analysis of the product showed C=80.8%, H=10.4%, N=0.9%, P=0.00% and molecular weight 475 calculated from freezing point depression. "The smallest gram molecule containing one atom of nitrogen must have a weight of about 1500."—J. C. D.

**Some limitations of the action of the so-called follicular hormone in birds.** Riddle (O.) & Tange (M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 648-652.

The authors summarize their results as follows: "Brief reference is made to the more important earlier studies on the action of a utero-stimulating substance in mammals. In a small group of tests of the utero-stimulating action of a placental extract, and of a substance prepared from the liquor folliculi of the sow by the Allen-Doisy method, we have obtained a few positive results—enlargement and hyperemia of the oviduct of virgin doves. This supplies the last necessary fact in proof of the lack of specificity, as between birds and mammals, of this substance. Heavy dosage failed to

effect a response in the virgin oviduct in some cases. Responses in the ovary and on sex behavior in virgin and mature doves have not been observed. An insufficient number of cases was studied but our results indicate a less ready, and a less varied, response of the bird to this substance than has been found for mammals."

—J. C. D.

**Gonads cross-transplantation in Sebright and Leghorn fowls.** Roxas (H. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 789-793.

The Sebright male has so-called "hen-feathering," the Leghorn male-feathering. In a series of carefully controlled experiments the testes of these two forms were interchanged. When the grafts took they gave cocks with normal sex and fighting instincts, but did not change the feathering characteristics of the normal males of the form in which they were growing.—J. C. D.

**Function of the ovary.** Zondek (B.) & Aschheim (S.), Klin. Wchnschr. (Berl.), 1926, 5, 400-404.

Zondek and Aschheim report that as implants of human ovarian tissue and placenta into mice are resorbed they may induce oestrous changes in the test animals which are reflected in the vaginal smear. Positive tests for active material in the implanted tissues are often obtained in this way. They report positive results from follicular fluid, the walls of large follicles, premenstrual corpora lutea, corpora lutea of pregnancy and placenta. They report negative results from ovarian tissues containing only small follicles and from corpora lutea removed during and just after menstruation. The tissue implants are not transplants. They are equivalent rather to injections of extracts.—E. Allen.

**Combating the insulin hypoglycemia.** Abelin (J.) & Goldener (J. E.), Klin. Wchnschr. (Berl.), 1925, 4, 1777-1778.

In earlier experiments the authors noted that phosphates increased hyperglycemia. This led them to the idea that phosphates might be used in combating the insulin hypoglycemia or rather to prevent insulin hypoglycemia by giving phosphates by mouth at the same time that insulin is administered. They used rabbits for this experiment, also for controls. In the controls, following the injection of 2 units of insulin (Eli Lilly and Co.) blood sugar dropped to 58 mg. per 100 cc. in 3 hours from the original figure of 81 mg. per 100 cc. in one rabbit; in another rabbit it was 85 at start, 2 units of insulin were injected and 1 gm. Na<sub>2</sub>PO<sub>4</sub> given by mouth in 10 cc. water — 1½ hours later blood sugar was 97, and 2½ hours it was still 85 mg. per 100 cc. In another rabbit fasting blood sugar was 83 mg. per 100 cc. 3 units of insulin injected and

only 10 cc. water given by mouth, 1½ hours later blood sugar was 56, in 2½ hours 56, in 3 hours 56 mg. per 100 cc. Other figures of similar nature are given, all indicating the prevention of a marked hypoglycemia by giving sodium phosphate in water by mouth.—H. J. John.

**On diabetic gangrene, with particular reference to value of insulin in its treatment.** Blotner (H.) & Fitz (R.), Boston M. & S. J., 1926, 104, 1155-1162.

The endocrine interest of this paper lies in the fact that since the introduction of insulin the mortality has gone from 25% down to 18% in these cases.—J. C. D.

**The insulin content of tumor tissue.** Cori (G. T.), J. Cancer Research (Lancaster), 1925, 9, 408-410.

Cori used the method of Doisy, Somogyi and Shaffer and found only traces of insulin in carcinoma of the breast, melano-sarcoma, leiomyoma of the uterus and lymphosarcoma of a dog.—J. P. S.

**The comparative action of pancreatic extract of Acanthias vulgaris and of insulin from beef (Extrait pancréatique de l'Acanthias vulgaris; son action comparée à celle de l'insuline du boeuf).** Ducloux (E.) & Cordier (Miss G.), Compt. rend. Acad. d. sc. (Par.), 1925, 181, 342-344.

The pancreatic extract of Acanthias produced hypoglycaemia when injected into guinea-pigs and rabbits, but the degree of hypoglycaemia could not be related to the weight of the animal. Intracardiac injections gave sensibly greater effects.—A. T. C.

**The use of insulin in eclampsia.** Stander (H. J.) & Duncan (E. E.), Am. J. Obst. & Gyn. (St. Louis), 1923, 10, 823-826.

Insulin treatment was used with beneficial results in acute cases of eclampsia. Six cases are reported upon in detail. The indications for the treatment are coma or semi-consciousness following a convulsion, a CO<sub>2</sub> combining power of 30 or below, and a considerable increase in blood sugar. The dosage (15-25 units) is regulated according to the degree of hyperglycemia, and the weight of the patient.—M. O. Lee.

**Diabetic and arteriosclerotic gangrene of the lower extremities.** Eliason (E. L.) & Wright (V. W. M.), Sur. Gynec. & Obst. (Chicago), 1926, 42, 753-768.

Analysis is given of a series of 45 cases of arteriosclerotic and 55 cases of diabetic gangrene of the lower extremities which have been amputated. One-fifth to one-fourth of all diabetics die of gangrene. The fifth and sixth decades are dangerous. Females die

slightly earlier than males. Diabetic gangrene appears on the average a decade earlier than the senile type.—A. T. C.

**Insulin in infant feeding.** Green (H.) & Robbins (G.), Boston M. & S. J., 1926, 194, 1162-1167.

Seven undernourished children in the hospital were given an injection of one unit of insulin for each 15 grams of carbohydrate in their diet. One received one unit for each 25 grams, and another one unit for each 50 grams. The authors summarize the results on these nine cases as follows:

"1. All cases gained with the exception of one, and this was due to a severe complication.

"2. In six cases the gains were striking.

"3. There was observed an improvement in the general condition of five cases.

"4. One case had a doubtful reaction.

"5. In two of the cases we not only stopped the progressive loss of weight but succeeded in obtaining a slight gain.

"We do not wish to leave the impression that insulin is the panacea for malnourished infants, but we are merely attempting to offer our own observations on a limited number of cases."—J. C. D.

**The proof that a hormone is concerned in external pancreatic secretion.** Ivy (A. C.) & Farrell (J. I.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 577-578.

If the jejunum is opened or transplanted and a pancreatic transplant is made, then HCl N/10 to N/120 applied to the jejunal mucosa will cause the pancreas to secrete actively. The latent period is three to six minutes.—J. D. D.

**Animal experiments on the physiological metabolic action of certain hormones. II. The action of choline in starvation (Tierexperimentelle Untersuchungen über die stoffwechsel-physiologische Wirkung bestimmter Hormone. II. Die Wirkung des Cholins im Hungerzustande).** Junkersdorf (P.) & Kohl (A.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 612-635.

Under choline action animals, whether starved or not, show hypoglycaemia, the intensity and duration of which depends on the state of nourishment. Liver glycogen is higher than in starved animals, and fat content lower. It is concluded that the hypoglycaemia is due to insulin action, produced by choline (secretin) action.—A. T. C.

**The hexophosphoric acid of blood in normal and diabetic organism and its relation to adrenalin and insulin.** Lawaczeck (H.), Klin. Wehnschr. (Berl.), 1925, 4, 1858-1861.

The author attempted to estimate the quantity of hexophosphoric acid in blood. He found that it was not soluble in Baryta, but by the reduction of barium he succeeded in separating the hexophosphoric acid as phosphoric acid from the free glucose of the blood, and then estimated its quantity as hexose by its reduction. The values of hexophosphoric acid found were 0.66 mg. per 100 cc. in one case of an old arteriosclerotic and 2 mg. per 100 cc. in a case of diabetes mellitus. Most cases were about 1 mg. per 100 cc., altho this first figure in the diabetic was high; further examination showed no variation from the non-diabetic, in fact, in one severe case of diabetes the figures were lower than in non-diabetics. The height of blood sugar bears no relation to the acid. When a high blood sugar in a diabetic is suddenly reduced, the h.p.a. also is somewhat diminished, though not always; at times the acid even rises.

The author studied the effect of adrenalin hyperglycemia to hexophosphoric acid. He injected in man 1 cc. of 1:1000 Merck adrenalin. In one hour blood sugar rose from the original figure of 111 to 171 mg. per 100 cc., slightly falling afterward; the h.p.a., on the other hand, dropped promptly in 15 minutes from 1.38 mg. per 100 cc. to 1.04 mg. per 100 cc., when at the end of the hour it rose to its original value, and at the end of 105 min. it rose to 1.54 mg. per 100 cc. Repeated trials showed the same. The only drawback to these experiments is that 50 cc. of blood is required for the acid determination.

The next experiment was performed with 100 units of insulin (Tetewop) on a dog. Blood sugar dropped from 71 to 61 mg. in 10 min. and to 54 mg. per 100 cc. in 25 min., whereas the h.p.a. rose steadily from 0.78 to 0.91 and 1.02 mg. per 100 cc., respectively. The author thinks this is a proof of the hypothesis that the breaking down of glucose goes thru the stage of h.p.a. combination.

In diabetic patients the author found two distinct groups: (1.) Those who, following insulin, present drop of blood sugar and rise of h.p.a., which later shows a compensatory drop, and (2.) group in which in 10 minutes after insulin a distinct decrease of h.p.a. takes place, d. e., a negative phase takes place very quickly, which the author explains as the organism reacting to insulin in an allergy manner. The antagonism between insulin and adrenalin in the carbohydrate metabolism shows itself also in the fact that such diabetics react to adrenalin thru a drop in the blood sugar figure, which was also observed by Brosamlen, Dresel and Kylin, and which was described by the latter authors as paradoxical adrenalin action, but which Lawaczeck considers not as such but as insulin action which is brought about by the allergically reacting organism, where the increase of adrenalin overcompensates quickly thru its liberation of insulin.

From these findings the author concludes that there are two forms of diabetes, the one which reacts to insulin in a normal way (drop of blood sugar, rise of hexophosphoric acid), which he thinks is true pancreatic diabetes with more or less destruction of insular tissue, and the other which reacts allergically, which he designates as functional diabetes which he thinks rests on a pathological balance between insulin and adrenalin. These diabetics respond to insulin with a lowering to adrenalin with an increase of hexophosphoric acid.—H. J. John.

**Experiments on the thoracic lymph of the dog. V. Influence of insulin and adrenine on the thoracic lymph of the dog (Untersuchungen an der Brustganglympe des Hundes. V. Ueber den Einfluss des Insulin und Adrenalins auf die Brustganglympe des Hundes).** Meyer-Bisch (R.), Günther (F.) & Bock (Dorothee), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 341-355.

Insulin produces a decrease of lymph flow and dilution of lymph. The chlorine content increases, calcium and potassium decrease. These changes are produced rather earlier and quite independently of the lowering of lymph sugar. Adrenine produces exactly opposite effects (except that calcium remains unaffected) and these can take place without any increase of lymph sugar.—A. T. C.

**Nitrogen balance on a low protein diet in a case of diabetes mellitus.** McClellan (W. S.) & Hannon (R. R.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 817-819.

The diabetic patient in bed was kept on a diet containing 20 grams of protein for 106 days. The fats and carbohydrates were varied to give 2000 calories. Insulin was used regularly. The nitrogen balance and weight were maintained on this diet.—J. C. D.

**The changing conception of diabetes as a disease.** Tuttle (G. H.), Boston M. & S. J., 1926, 194, 931-932.

In the light of recent pathological studies diabetes is to be looked on as a functional disorder in which possibly the damage in the islet tissue is a secondary result rather than a primary cause.

—J. C. D.

**Transplantation of a human parathyroid in a case of chronic tetany in an adult.** (Tetanie Chronique Des Adultes et Transplantation de Parathyroïdes). Frugoni (C.) & Scimone (V.), with a note by Comolli (A.), Presse Méd. (Par.), 1926, 34, 355-358.

These authors report a case of chronic tetany in an adult. The blood calcium was 9.2, 8.7 and 9 mgs. per 100 c.c. and the electrical excitability of the muscles was low. It was thought at first the patient was an epileptic as well, but the pupils did not dilate. A parathyroid from a young girl undergoing an operation

for a parenchymatous goitre was transplanted into the vaginalis of the testicle using Voronoff's technique. The parathyroid was fixed by means of catgut. The graft is palpable at present. The symptoms of tetany disappeared and the calcium of the blood was increased, being 9.4, 10.8 and 10.9 per 100 c.c.—E. Larson.

**Effect of parathyroid hormone on certain signs and symptoms in tuberculosis.** Gordon (B.), (Roark (J. L.) & Lewis (A. K.), J. Am. M. Ass. (Chicago), 1926, 86, 1683-1686.

To a series of sixty tuberculous patients, parathyroid hormone injections were given. There followed improvement in strength, increased warmth, and lessened muscular and pleuritic pain. In some instances, there was also a favorable effect on laryngeal tuberculosis. The effect on cough was variable; the dry hacking cough was often aggravated; the productive coughs were often less troublesome during treatment, and there was decreased expectoration. There was a favorable effect on dyspnea. The most striking objective feature was in the control of pulmonary hemorrhage. This was relieved quite constantly. There was also a decrease on the edema of the arytenoids and other structures involved in laryngeal tuberculosis, with some evidence of healing. In pleurisy and pulmonary congestion there was evidence of decreased râles following the administration of the parathyroid hormone. In the roentgen-ray examination, there was a suggestive clearing of the lung fields, but no evidence of calcification. In general there was a favorable effect on the condition of the patients, as shown by increase of appetite, gain in weight, and lowered temperature and pulse rate. The untoward features were arthritic pains, dryness of the throat, increased coughing, palpitation, weakness, and periods of elevated temperature and pulse with loss of weight and appetite, and were usually due to overdosage. These phenomena were generally relieved following the withdrawal of the medication, and seldom reappeared during moderate dosage. There appears to be no evidence that a favorable effect on pulmonary tuberculosis is obtained from maintaining a high calcium content in the circulating blood. The authors comment on the desirability of caution in the interpretation of results in so few patients.—R. G. H.

**The spasm of tetany considered as a disturbance of the physiology of muscle.** Martin (J. P.), Quart. J. Med. (Oxford), 1926, 19, 311-321.

Martin presents evidence which indicates that the spasm of tetany is intrinsically muscular. He puts forward the theory that this spasm is due to the breaking down by chemical influences of the lactacidogen (glycogen) of the muscles involved. Calcium at its normal concentration in the blood inhibits this breakdown, but a small reduction in calcium content removes a great part of this

inhibitory action. Lactacidogen breaks down more easily when the hydrogen-ion concentration is reduced; the effects of alkalosis in helping to cause tetany and of acidosis in relieving it may be thus explained.—J. P. S.

**The reality of action of a thymus diet on growth and development of frog larvae (Ueber das Wesen der Wirkung der Verfütterung von Thymusgewebe auf Wachstum und Entwicklung von Froschlarven).** Abderhalden (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 324-332.

Tadpole experiments are not suitable to decide the question of the internal secretion of the thymus.—A. T. C.

**Relation of suprarenal cortex to thyroid and thymus glands.** Marine (D.), Arch. Path. & Lab. Med. (Chicago), 1926, 1, 175-179.

The failure of involution or the actual regeneration of the thymus in exophthalmic goiter, acromegaly, Addison's disease and status lymphaticus, suggested to Marine that the thymus must play some important, though not vital, role, in the maintenance of the balance of action of other internal secretions. In 66 thyroidectomized rabbits of known age, the involution of the thymus was hastened. For these and other reasons cited from the literature, Marine is convinced that the thyroid gland is necessary for normal thymus growth and function. In a "large series" of rabbits and rats it was shown that suprarenalectomy exerts a powerful stimulating influence on the thymus: in sexually immature animals by stimulating further growth; in older animals with highly involuted thymuses, by bringing about a regeneration of the thymus. The regeneration includes both medulla and cortex of the thymus. Gonadectomy alone delays involution of the thymus, probably by way of suprarenal involvement. Gonadectomy and suprarenalectomy combined causes more marked regeneration of the thymus than either of these alone. Thyroidectomy prevents the regeneration of the thymus which usually follows suprarenalectomy. A functionally active thyroid, therefore, appears necessary for thymic regeneration which follows suprarenalectomy. The combined effect of suprarenalectomy and gonadectomy results in certain lymphoid and thymus hyperplasia in rabbits and rats which persists until regeneration of accessory interrenal tissue corrects the physiologic defect. The syndrome thus experimentally produced resembles status lymphaticus and is believed to depend mainly on a partial loss of certain functions in the interrenal and sex glands rather than of the chromaffin tissue. The normal and abnormal lymphoid and thymic hyperplasias of infancy and childhood are believed to be manifestations of a functional under-development of the interrenal and sex glands of varying intensity. The so-called lymphatic con-

stitution which underlies or accompanies exophthalmic goiter and Addison's disease also appears to be dependent on a partial suppression of certain functions of the interrenal and sex glands.—J. P. S.

**The influence of thyroid feeding on the Islets of Langerhans in the guinea pig.** Cameron (G. R.), J. Path. & Bact. (Edinb.), 1926, 29, 177-183.

Twenty-five guinea pigs were fed with thyroid extract for periods varying from 6 to 63 days, and 40 guinea pigs of approximately the same size were used as controls. At the end of the experiments the animals were killed, the pancreas was removed and weighed and the ratio of islet to total pancreatic tissue was determined by Vincent's method. On the basis of these experiments Cameron concluded that in the guinea-pig feeding with thyroid extract causes hypertrophy of the pancreas and an increase in the proportion of islet tissue.—J. P. S.

**The influence of the autonomic nervous system on the function of the thyroid gland.** Crawford (J. H.) & Hartley (J. N. J.). J. Exper. Med. (Balt.), 1925, 42, 179-191.

The authors of this paper undertook to investigate the influence of stimulation and section of the various nerves going to the thyroid gland on its histological appearance with the hope of throwing some light on the mechanism of control of its function. Because of the marked differences which were found to occur in the glands of different rabbits, the method used was that of first removing one lobe before stimulating or dividing the nerves going to the other. Experiments were carried out in which all combinations of stimulation and section of sympathetic and vagus branches were tested. For study the tissues were fixed in Muller's fluid with 5 per cent formalin and the sections stained with iron hematoxylin and eosin. Careful examination revealed no changes in the histology of the gland following either section or prolonged faradic stimulation of its nerve supply.—I. M.

**The innervation of the thyroid (Zur Innervation der Schilddrüse).** Engel (W.), Arch. f. d. ges. Physiol. (Berl.), 1926, 211, 433-439.

Adrenine produces dilatation of the thyroid blood vessels when injected locally intravenously, whence it is concluded that the Sympathicus is the vasodilator and secretory nerve of the gland.

—A. T. C.

**Interrelationship of Basedow's and Addison's diseases (Maladie de Basedow et Addisonisme).** Etienne (G.) & Richard (G.), Rev. franç. d'Endocrinol. (Par.), 1926, 4, 1-11.

As evidence of interrelationship between the thyroid and the adrenals the authors cite two cases of well marked Addison's syn-

drome following the incidence of, and disappearing after the successful treatment of, exophthalmic goiter. In a third case in which the development of Addison's disease preceded that of exophthalmic goiter treatment failed to forestall a fatal issue.—R. G. H.

**Surgical care of the toxic thyroid.** Frank (L. W.), Southern M. J. (Birmingham), 1926, 19, 450-453.

The author summarizes his views as follows:

Rest in the hospital is essential for the proper pre-operative care of the toxic thyroid, and by such treatment the condition of the patient is greatly improved. Hospitalization may be necessary from a few days to several weeks. During this period the heart and kidney function and the nervous stability of the patient should be carefully evaluated. The result of such observation combined with a study of the basal metabolic rate gives us a fairly accurate index of the severity of the intoxication. By the administration of iodin in some form severe cases may sooner be brought to a condition for safe operation. Local anesthesia reinforced with gas-oxygen is the best anesthetic for such cases. By the employment of the anoxic method of Crile certain otherwise inoperable cases may be successfully operated.—J. C. D.

**The effect of hypophysin and thyroid extract on secretion of urine (Die Wirkung von Hypophysin und Thyreoidin auf die Diurese).** Frey (E.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1926, 110, 329-334.

The colloidal constituents of the blood were unaffected when pituitary extract was injected into the circulation of rabbits; urine secretion was increased by vasodilatation and increased blood flow. Thyroid extract caused the colloids of the blood to rise, cessation of urine secretion, and oedema formation.—G. E. B.

**Studies on experimental cretinism. II. Nutritional disturbances of bones.** Kunde (Margarete M.) & Williams (L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 812.

Rabbits and rats after thyroidectomy develop a condition similar to rickets though fed an adequate diet.—J. C. D.

**Studies on experimental cretinism. III. Nutritional disturbances, pellagra and xerophthalmia. IV. The influence of thyroidectomy on the central nervous system.** Kunde (Margarete M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 812-813.

Xerophthalmia and the lesions characteristic of pellagra appear in thyroidectomized rabbits kept on a diet adequate for the controls.

Cretin rabbits were carried through the growth period with doses of thyroxin or dessicated thyroid. Thyroid treatment was then

stopped. The animals developed a progressive paralysis starting in the hind quarters. Autopsy showed lesions in the spinal cord.

—J. C. D.

**The transplantation of parathyroids in partial thyroidectomy.** Lahey (F. H.), *Surg. Gynec. & Obst.* (Chicago), 1926, **42**, 508-509.

Parathyroids should be carefully searched for in the specimen following operation, and, if found, transplanted. The belly of the sternomastoid is the most convenient place into which to transplant them; care should be taken to see that the cavity into which they are transplanted is dry.—A. T. C.

**Studies on compensatory hypertrophy of the thyroid gland. VII.**

Further investigation of the influence of iodine on hypertrophy of the thyroid gland with an interpretation of the differences in the effects of iodine on the thyroid under various pathologic conditions. Loeb (L.), *Am. J. Path.* (Boston), 1926, **2**, 19-32.

Loeb carried out seven series of experiments on 148 guinea pigs, of which 72 received potassium iodide after previous removal of the greater part of the thyroid, and 76 served as controls. Six types or grades of hypertrophy were distinguished. On the basis of these experiments "it can be definitely stated that potassium iodide does not prevent the hypertrophy of the thyroid gland in the guinea pig which follows extirpation of a great part of the thyroid gland." On the contrary, in all of Loeb's experiments, the average of hypertrophy was greater in the animals which received potassium iodide than in the control animals. There are, in addition to the amount of thyroid removed and the amount of iodine fed to the animals, other variable factors which influence the degree of hypertrophy following extirpation, such as seasonal changes and others which are unknown. As in former experiments, Loeb found that the average hypertrophy less marked in the summer months than that in experiments carried out during the winter. On the basis of his results, Loeb offers a tentative explanation of the influence of iodine on the structure and function of the thyroid.—J. P. S.

**Further observations on autotransplantation and homoiotransplantation of thyroid gland in the guinea pig.** Loeb (L.), *Am. J. Path.* (Boston), 1926, **2**, 99-110.

Loeb followed the successive changes in auto- and homoiotransplants of thyroid tissue in guinea pigs for periods up to 17 days after transplantation. He observed significant differences between the two types. There is a gradual elimination of those factors which distinguish an early auto-transplant from normal organ. By the gradual disappearance of fibrous tissue, some fat tissue and the accumulations of lymphocytes, the tissue relations in the transplant tend to attain the same mutual equilibrium which

exists in normal organs. The normal equilibrium between tissues is determined by auto-substances which in this case are given off by acinus cells and which act upon the connective tissue cells, blood vessels and lymphocytes. The large majority of homoio-transplants, on the other hand, can be arranged in three types, ranging from complete destruction to a condition approaching those found in syn-genetic-transplants, according to the severity of the destruction caused mainly by the activity of the connective tissue and lymphocytes of the host. While these differences in the behavior of the transplants are essentially graded in accordance with the genetic relationship of donor and host, there are some indications that non-genetic variable factors (e. g., age, pregnancy, etc.) may to a certain extent modify the intensity of the reaction.—J. P. S.

**Hyperthyroidization experiments on dogs. III. Thyroid and carbohydrate tolerance (Hyperthyreoidisationsversuche an Hunden. III. Schilddrüse und Kohlenhydrattoleranz).** Mark (R. E.), Arch. f. d. ges. Physiol. (Berl.), 1926, **211**, 523-547.

A dose of 10 grams sugar per kilo body-weight produces alimentary hyperglycaemia in normal dogs during 4 hours. Artificially hyperthyroidized dogs show a markedly increased hyperglycaemia, while thyroidectomized dogs show less effect than the normal animals. Hence intermediate carbohydrate metabolism is linked with thyroid action.—A. T. C.

**Hyperthyroidization experiments on dogs. IV. Action of iodine-poor thyroid preparations (Hyperthyreoidisationsversuche an Hunden. IV. Wirkung von jodarmen Schilddrüsenpräparaten).** Mark (R. E.) and Stradal (A.), Arch. f. d. ges. Physiol. (Berl.), 1926, **212**, 486-500.

Both peroral and subcutaneous administration of large amounts of an almost completely iodine-free thyroid preparation produced no hyperthyroidization.—A. T. C.

**The influence of the thyroid on carbohydrate metabolism (Thyroid in normal cases and in exophthalmic goiter under Röntgen irradiation).** Maselli (D.), Problemi di nutrizione (1924), **1**, 367-380; Ber. ges. Physiol. exptl. Pharmakol. (1925), **31**, 69; Abst. Chem. Absts., **20**, 1652.

Irradiation of normal thyroid in dogs produced hyperglycemia without glucosuria. Irradiation of other parts of the body did not influence carbohydrate metabolism. A similar effect was produced by Röntgen irradiation of the thyroid in a patient with exophthalmic goiter. No histological changes of the thyroid were observed.

**Exophthalmic goiter in the Pacific Northwest.** Mason (J. T.), *Surg., Gynec. & Obst. (Chicago)*, 1926, 42, 663-666.

Good results are claimed with Lugol's solution. Removal of a small portion of thyroid at ligation after a few days' treatment with the solution, and partial thyroidectomy in the same patient after six weeks' intensive treatment showed histologically conversion of the typical picture of exophthalmic goiter into a colloid gland with very little hyperplastic tissue.—A. T. C.

**The treatment of exophthalmic goitre.** Moorhead (T. G.), *Practitioner (Lond.)*, 1926, 116, 402-410.

This is a plea for the medical treatment of goitre. The patient is placed in a nursing home, the thyroid treated with ice-bags for a week and then with x-ray at intervals for a month. The patient rests at home a month. Then the x-ray treatment is repeated. Lugol's solution is helpful in the early part of the treatment.

—J. C. D.

**Endemic goiter and intelligence of school children.** Oleson (R.) & Fernald (Mabel), *Public Health Reports (Washington)*, 1926, 41, 971-986.

Three thousand seven hundred and ninety-six children in the sixth grade of the Cincinnati public schools were included in a study having for its purpose the determination of whether endemic goiter influences intelligence. Some degree of enlargement was found in 25.2% of the white boys and 39.6% of the white girls included in the survey. Two indices were utilized in determining the intelligence of the children studied: First, the information afforded by school retardation or advancement as indicated by age; second, the records of a standard group test decided to measure intelligence. Analysis of chronological age data, indicative of school retardation or advancement, failed to reveal significant variations between thyroid-normal and thyroid-enlarged children. A comparison of the percentile ranks of the thyroid normal and the thyroid enlarged failed to show differences of sufficient magnitude to warrant the conclusion that the thyroid normal have a keener mentality than the thyroid enlarged. Children with marked thyroid enlargements were apparently slightly less intelligent on the average than those with normal or slightly enlarged thyroids. However, the number of children with marked thyroid involvement was relatively small, suggesting the desirability of further observances on children with marked thyroid enlargements before drawing conclusions concerning the influence of thyroid size upon intelligence.

**A simple and accurate method of determining basal metabolic rate.** An electrometric (Katharometer) procedure. Rabinowitch

(I. M.), & Bazin (Eleanor V.), Can. Med. Ass. J. (Montreal), 1926, 16, 638-646.

The katharometer has been used for testing permeability of balloon fabric, for measurement of composition of alveolar air, and as a flue gas tester. It is here applied to measure the percentage of carbon dioxide in expired air, which is passed through two opposite wires of a Wheatstone bridge circuit and affects the heat generated in them, so giving a galvanometer reading proportional to the carbon dioxide present. The instrument is placed in circuit with an air meter, and, from the CO<sub>2</sub> percentage and total volume expired the basal metabolic rate is determined. The results, compared with those determined with a Tissot gasometer and Haldane gas apparatus, show extremely good agreement, and this open circuit method seems to give greater accuracy than the clinical closed circuit instruments.—A. T. C.

#### **The value of iodine in the surgical treatment of exophthalmic goiter.**

Richardson (E. P.), Boston M. & S. J., 1926, 194, 1066-1071.

The author emphasizes from his own experience (1) the benefits of Lugol's solution in reducing the operative risk in such cases; (2) the temporary character of the action of the solution so that the patient must be carefully followed and the operation done at the most favorable moment; (3) that a more extensive operation can be performed under such conditions than was safe without the preliminary iodine treatment; (4) that surgically the thyroid case remains a grave risk even though markedly improved by the iodine treatment.

#### **A local sympathetic reflex in hyperthyroidism (Ueber den regionär-vegetativen Reflex bei Hyperthyreoidismus).** Serejski (M.), Detusche med. Wehnschr. (Berl.), 1926, 10, 1-4.

The author reports a diagnostic test for "hyperthyroidism" that, in his experience, is often useful in detecting latent cases. This is a local erythema on sweating in the region of the thyroid gland following the injection of a test dose of pilocarpine. Five illustrative cases are reported.—R. G. H.

#### **Three cases of thyroid metastasis to bones.** Simpson (W. M.), Surg., Gynec. & Obst. (Chicago), 1926, 42, 489-507.

There is no such entity as "benign metastasizing goiter;" the use of this confusing term should be abandoned. Two of the cases, reported showed osseous metastases of microscopically benign thyroid tissue, associated with clinically negative goiters. Both subsequently developed carcinoma of the thyroid and died within two years. In most previously reported cases authors have published shortly after discovering the innocent microscopic appearance of the

metastases, and without waiting to learn the outcome. Many cases have been recorded in which microscopical examination of tissue from the metastasis revealed normal thyroid structure, while histological study of tissue from the thyroid gland showed areas of undoubted carcinoma. Seventy-seven previously published case reports are abstracted.—A. T. C.

**Studies of hyperthyroidism. II. The significance of changes in the thymus glands of thyroid-treated frog tadpoles.** Speidel (C. C.), Am. J. Anat. (Phila.), 1926, 37, 141-157.

The normal thymus glands of tadpoles of the green frog (*Rana clamitans*) consist almost entirely of lymphoid aggregations interspersed with large blood sinuses. They function as lymphocytopoietic organs. Administration of thyroid extract to the tadpoles brings about definite changes in the thymus glands. Lymphocytes, especially the larger ones, are stimulated to mitotic proliferation. The blood sinuses become reduced in size. The hyperplasia of lymphoid cells is followed by their extensive ameboid migration into the blood sinuses and thence into the general circulation. The increased production of lymphocytes is not peculiar to the thymus glands, but occurs in many regions of the body. There is, therefore, a general lymphoid reaction to hyperthyroidism. Excess thyroid autacoid acts upon various types of undifferentiated cells to cause mitotic division. Of the blood cells lymphocytes are the relatively undifferentiated type. In the tadpoles and frog they function as blood mother-cells for erythrocytes, granulocytes and monocytes. The new metabolic conditions of hyperthyroidism establish a need for more erythrocytes, as well as a granulocytes and monocytes. The lymphoid hyperplasia is regarded as the preliminary phase of the response on the part of the body to supply these cell types. The possibility is suggested that the lymphoid hyperplasias associated with human exophthalmic goiter, which reach their extreme form in *status lymphaticus*, are of the same fundamental nature and significance.—Author's Abstract.

**Iodin in the treatment of hyperthyroidism.** Thomas (H. M.) & Reinhoff (W. F.), South. M. J. (Birmingham), 1926, 19, 87-94.

A careful review of the important literature with a list of references is followed by a report on 29 cases. Lugol's solution was given to patients kept in bed and fed a liberal diet. The average age in the series was 33 years. There was an average reduction of 36.8% in the basal metabolic rate. The maximum effect occurred on the average 11.8 days after the administration was begun. These subjects were operated on. They showed much less post-operative loss in weight than those operated upon without preliminary iodin-therapy. In a series of 8 cases part of the thyroid was removed before Lugol's solution was given. A second operation was done

after a course of iodine treatment and the portions of thyroid excised at each operation compared histologically. The author's important conclusions are that iodin produces a marked clinical improvement in cases of Graves' disease and causes a reversion in the thyroid gland of Graves' disease from a state of hyperplastic over-activity to a condition approximating a thyroid gland from a normal individual (having once passed through the hyperplastic stage thereafter the quiescent gland probably always contains an excess of colloid). This effect is rarely permanent and should be closely followed by appropriate surgical procedures. In a small but definite number of cases of exophthalmic goiter the administration of iodin is unattended by clinical improvement. In a very small portion of apparently normal though hypersensitive persons iodin may produce the clinical picture of hyperthyroidism or possibly even Graves' disease. Finally, it may be regarded as proved that although iodin has not yet been shown to effect a permanent cure, it is an indispensable adjunct to safe surgical procedure in the treatment of exophthalmic goiter.—J. C. D.

A relation between experimental hyperthyroidism and barring in poultry. Torrey (H. B.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 23, 536-537.

Dessicated thyroid added to the diet or thyroxin injections produce changes in the feather structure. The uniform broad lacy borders formed of naked barbs found in some feathers in the male are modified by an overgrowth of the barbules to form a scalloped edge. These scallops correspond closely with the pigment bars.

—J. C. D.

Inflammations of the thyroid gland. Watkins (J. T.), Ann. Clin. Med. (Balt.), 1926, 4, 628-642.

It is concluded that the thyroid gland is very infrequently the site of inflammatory processes. Practically all types of inflammatory reaction may occur in the gland. Chronic interstitial lesions are most frequent and in most instances are associated with other processes which dominate the clinical picture, viz., simple hypertrophy, parenchymatous hyperplasia, adenomatous hyperplasia, colloid goiter, etc. Varying grades of hypofunction, even marked myxedema, may follow any of the types of inflammatory reaction. What has been called thyroiditis by many pathologists is probably only an expression of lymphatism.—R. G. H.

The relation of the thyroid gland to the surface tension of the blood plasma. I. The effect of thyroidectomy. Wilhelmj (C. M.) & Fleisher (M. S.), J. Exper. Med. (Balt.), 1925, 63, 179-193.

The authors report their results from a series of experiments in which the effect of thyroidectomy on the surface tension of the

blood plasma was studied. The surface tension of arterial blood plasma was determined by the du Nouy tensiometer in 41 control and 42 thyroidectomized male guinea pigs at various intervals following the operation. In the majority of the experiments the plasma was allowed to stand 20 minutes before determinations were made, but in the remainder readings were made immediately and at the 20-minute period as well in order to determine the time-drop. A gradual elevation of the surface tension of the plasma was found to occur as a result of thyroidectomy, reaching its height in from 19 to 22 days. The time-drop (difference between the initial and 20 minute determinations) was greater in the plasma from normal than in that from operated animals. The average surface tension values for the 41 controls was 53.2 dynes while that of the operated animals was 57.3 dynes. The authors suggest that these changes are due to a decrease in the amount of certain normally occurring surface-active substances, the production of which is dependent upon the thyroid gland.—I. M.

**The relation of the thyroid gland to the surface tension of the blood plasma. II. The effect of the administration of thyroid extract and thyroxin.** Wilhelmj (C. M.) & Fleisher (M. S.), *J. Exper. Med.* (Balt.), 1925, **63**, 195-205.

The object of the experiments presented in this communication was that of determining the effect of thyroxin extract administration on the surface tension of blood plasma in normal guinea pigs. The surface tension of the plasma from arterial blood was measured in 27 animals before and again after the administration of 1 to 1.2 mg. of thyroxin over a period of 4 or 5 days. Of these animals 20 showed a decrease in surface tension of the plasma ranging from 1.9 to 13.9 dynes with a mean value of 5 dynes. The remainder showed little or no change. Of seven control animals bled at the same time and kept under identical conditions, six showed variations in the surface tension of the plasma ranging from 0.5 dyne increase to 0.6 dyne decrease on the two determinations, while one showed a fall of 1 dyne. Two animals given thyroid extract over a period of 10 days gave values considerably below normal. The hypothesis is suggested by the authors that the changes observed are due to an increase in some normally occurring surface-active constituents, which are produced as a result of increased cellular metabolism.

**A reticle of endothelial cells in the thyroid and parathyroid.** Williamson (G. S.) & Pearse (I. H.), *J. Path. & Bact. (Edin.)*, 1926, **29**, 167-169.

Williamson and Pearse previously presented evidence that a lymph sinusoid is the essential feature of the parenchyma of the

thyroid gland. In this paper they describe an endothelial reticle in the thyroid and parathyroids composed of fused processes of adjoining endothelial cells which may be granular and appear to be distinct from the endothelium of the web of blood capillaries which enfolds the follicles. These large cells they believe to be similar to the Kupfer cells of the liver and they identify this interlacing meshwork with the reticulo-endothelial system of Aschoff. The contents of the cytoplasm of the reticulo-endothelial cells vary with variations in the functional activity of the thyroid and parathyroid glands.—J. P. S.

**Thyroid opotherapy in dyspituitarism.** Wynn (J.), J. Am. M. Ass. (Chicago), 1926, 86, 820-822. Abst. A. M. A.

The author records a case of dyspituitarism which has been under observation for twenty-eight months and in which the correlation between clinical status and the amount of thyroid extract ingested is well illustrated. The patient's imperfect co-operation during the earlier months of treatment afforded a striking demonstration of the effects of both insufficient and excessive opotherapy. Thyroid extract and the whole pituitary substance were administered orally, in capsules. The daily doses were divided into three equal parts, given morning, noon and night. The daily dose of whole pituitary substance varied from 9 grains to 15 grains (0.06 gm. to 0.9 gm.). It was discontinued after five months. Thyroid extract was given in daily doses of  $1\frac{1}{2}$  to 8 grains (0.09 to 0.5 gm.). Discontinuance of the thyroid extract invariably was followed by a return of symptoms. Since March 15, 1924, a daily dose of 6 grains (0.4 gm.) has been taken with no periods of interruption. No occasion has arisen for other medication. On this treatment, the man has remained symptom-free for thirteen months.

# Endocrinology

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## GUANIDINE AND THE PARATHYROIDS

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Even a cursory examination of microscopic sections from the parathyroids removed at the routine autopsies is sufficient to make one realize how scanty is the basis upon which any histological interpretation may be made.

In even a small collection of sections from the parathyroids, the variety of appearances which are usually seen, suggests that factors either normal or pathological have the power to change very appreciably the state of the circulation in the glands, the amount of globulation in the epithelial cells, and the proportion of the eosinophile cells present.

These are the problems to be considered.

In order to establish the necessary histological basis for further interpretation, it is necessary to correlate the functional states of the parathyroids with some definite histological appearances. As a result of the work of Paton and Findlay, and their co-workers, it is known that varying degrees of hyperactivity can be induced by the injection of

guanidine. Our initial task, therefore, is to find some distinct histological features indicating hyperactivity of the glands.

Since the following experiments are based on the findings of Paton and Findlay, it is necessary to keep in mind their conclusions. They are of the opinion that the parathyroids control the metabolism of guanidine in the body, by preventing its development in excessive amounts. Since, according to these authors, guanidine is responsible for the maintenance of muscle tone, the glands exercise a regulative action over them.

Schafer considers that the parathyroids produce an autocoid which is passed into the blood stream. This autocoid promotes protein metabolism and enables intermediate products such as guanidine to be further metabolised. Collip has partially isolated this active principle.

The conclusions of these workers suggest that, by the introduction of a guanidine compound into the animal, its parathyroids must become more active to counteract the effects of the guanidine compound. If this hypothesis be correct, a series of injections at various intervals would give a microscopic picture of the gland at rest, in various stages of activity, or perhaps, even, in a state of functional strain.

#### HISTOLOGY

The histology of the parathyroids has been described in detail by Sandstroem, Kohn, Welsh, Benjamins, Erdheim and Thompson. Briefly, their findings are that the cells are divided into two types.

There are the comparatively small cells with large, deeply staining nuclei, colorless cytoplasm and a distinct cell border. These cells constitute by far the greater part of the glands.

In the other division are the large eosinophilic cells with small nuclei, granular cytoplasm, and a distinct cell outline. These cells are seldom numerous in normal glands, and in some sections they may be absent.

It is often possible to find cells with features of both types. This would seem to suggest that the variations only signify different phases of functional activity in a single type of cell,—which is the view held by Schafer.

Another important feature is that the cells and the connective tissue of the parathyroids may contain a considerable amount of fat (Thompson, Benjamins and Welsh). The intra-cellular fat in the parathyroids of the rabbit takes the form of numerous and conspicuous large globules.

#### EXPERIMENTAL DATA

Only the microscopic features of the parathyroids are being discussed here, as the other aspects of the effects produced by guanidine injections are dealt with fully by Paton and Findlay, and their co-workers.

Adult rabbits were injected, chiefly intravenously, with a 5% solution of guanidine nitrate in normal saline. The tissues were fixed in Helleys fluid. The sections were stained with hemalum and eosin, and with acid fuchsin and methyl green.

In order to investigate the nature of the globules present in the parathyroids, half of each glandule, from a number of animals, was fixed according to Regand's method and the sections were stained with acid fuchsin and methyl green. By so doing, lipoid substances within the gland, to a large extent, were retained and demonstrated.

The following represents a summary of the experiments together with the macroscopic and the microscopic appearances of the parathyroids:

R. 15. 850 gms. aet 4 months.

0.4 gms. per kilogram of body weight were injected subcutaneously. The animal died in 18 hours.

##### *Macroscopic Examination.*

*Parathyroids:* Intensely congested; one looked haemorrhagic. (Congestion was not so marked a feature of the other organs.)

##### *Microscopic Examination.*

*Parathyroids:* The glandules are intensely congested. The usual large globules are rare (Fig. 1) but small ones are present in appreciable numbers. The cells are pale, indefinite and swollen. Nuclear chromatin is not so abundant as usual. Occasionally there are nuclei showing a distinct achromatosis. A number of the smaller cells possess very dark nuclei.

R. 16. 830 gms. aet 4 months.

0.2 gms. per kilogram of body weight were injected subcutaneously. The animal died in 20 hours.

##### *Macroscopic Examination.*

*Parathyroids:* No abnormality is obvious to the naked eye.

*Microscopic Examination.*

*Parathyroids:* These are congested. Although there are very few large globules, those of the smaller size are quite numerous.  
R. 13. 1590 gms. aet 6 months.

Injected intravenously with 0.1 gm. per kilogr. of body weight.  
Killed in 24 hours.

No abnormality is obvious to the naked eye.

*Microscopic Examination.*

*Parathyroids:* There is no obvious congestion. The scarcity of large globules is a conspicuous feature. With the oil immersion lens (1/12) numerous small globules are visible. In general, the cells are large, swollen, granular, and contain numerous small globules.

N. 314.

Injection of 0.5 gms. per kilogr. of body weight. Killed in 48 hours.

There are no obvious macroscopic abnormalities.

*Microscopic Examination.*

*Parathyroids:* The large colorless cytoplasmic globules are abundant (Fig. 2). Very few of the smaller and more opaque globules are to be seen.

R. 17. 800 gms. aet 4 months.

Injected intravenously with

0.1 gms. on 1st day. } Per kilogr. of  
0.17 gms on 4th day. } body weight.

Killed on 5th day.

*Microscopic Examination.*

*Parathyroids:* The cells are massed together and contain very deeply staining nuclei. The cytoplasm is almost uniformly finely globulated. There is a conspicuous scarcity of the large globules. Congestion is only slight.

R. 12. 1440 gms. Adult.

Intravenous injection of 0.1 gms. per kilogr. of body weight.  
Killed on the 8th day.

On post-mortem examination the parathyroids seemed large and were pale.

*Microscopic Examination.*

*Parathyroids:* The cells have deeply staining nuclei and are extremely vacuolated. In the majority these vacuoles occupy the greater part of the extra-nuclear cell structure. Smaller globules are of frequent occurrence.

In sections stained with hemalum and eosin, the cytoplasm of many cells contains opaque granular dark staining masses. Sections stained with acid fuchsin and methyl green show acidophilic granules in the epithelial cells, especially in those which border on capillaries.

There is no congestion.

R. 18. 730 gms. Adult.

Received intravenous injections of

0.05 gms. on 1st day } Per kilogr. of  
0.1 gms. on 6th day } body weight.

Killed on the 9th day.

*Microscopic Examination.*

*Parathyroids:* While the large globules are not so abundant as usual, the cytoplasm of the cells contains many of the smaller type. The nuclei have stained deeply. The cell boundary is distinct.

R. 14. 1370 gms. aet 6 months.

## Intravenous injections of

0.06 gms. on 1st day	}	Per kilogram of body weight.
0.08 gms. on 4th day		
0.1 gms. on 11th day		
0.1 gms. on 14th day		
0.12 gms. on 18th day		
0.13 gms. on 20th day		
0.15 gms. on 25th day		

0.19 gms. on 27th day

Throughout the latter part of this experiment muscular spasm was elicited by the slightest stimulus. The animal was killed 2 hours after the last injection while in tetany.

*Post-Mortem Appearances.*

*Parathyroids:* Pale and enlarged.

*Microscopic Examination.*

*Parathyroids:* The granularity of the cells is very marked, while the amount of globulation is only moderate. The cells are large and indefinite, while the nuclei are granular, and stain less deeply than usual (Fig. 3). In many cases, there is distinct evidence of hyperplasia. On the whole, congestion is fairly pronounced.

(N. B.—In all except R. 14, eosinophilic cells are rarely seen, while in R. 14 they are present in appreciable numbers.)

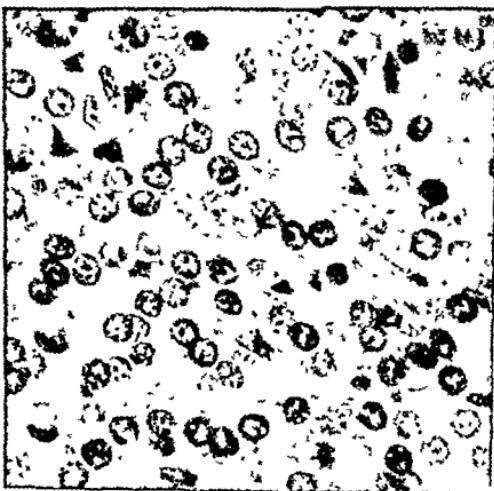


Fig. 1 R. 15: x 550 Hemalum and Eosin. The almost complete disappearance of globules from the gland 18 hours after the injection of guanidine nitrate

**DISCUSSION**

What information have these experiments produced?

To answer this, we must consider the relationship of the cytoplasmic globules with parathyroid activity and with guanidine. The appearance and disappearance of these globules after guanidine injections, and the altered appearance of the parathyroid cells, indicate that some relationship does exist.

## GUANIDINE AND THE PARATHYROIDS

A section of the normal glandule of a rabbit exhibits a most extensive globulation of the cytoplasm, the globules occupying the greater part of the cytoplasm. These are of a fatty nature. (Thompson, Benjamins and Welsh.)

After the injection of guanidine nitrate, these large globules disappeared in 18 hours (Fig. 1). In their stead, were the very minute globules which at first were recognized only by an examination with the oil immersion lens (1/12).

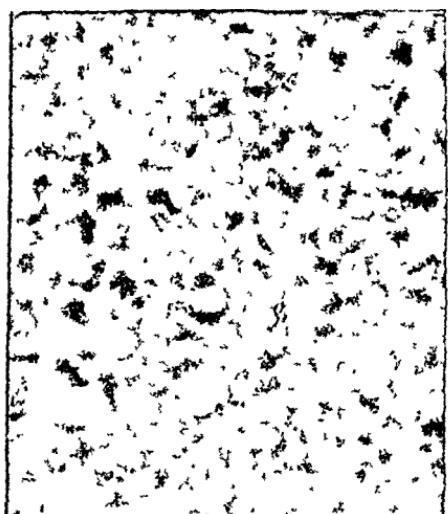


Fig. 2. N. 314: x 500. Hemalum and Eosin. In 48 hours globulation has returned to the normal amount, as seen in the parathyroids of the normal rabbits



Fig. 3. R. 14: x 650. Hemalum and Eosin. The cells are large, the cytoplasm finely globulated, and nuclei not as deeply staining as usual.

Up to 48 hours, the picture was similar. At 48 hours, the gland had recovered its normal globulated appearance. The small globules had diminished in number. Eight days after a single injection, the glands had an appearance similar to that seen in 48 hours (Fig. 2).

It therefore would seem probable that the variations in size and number of globules within the cells of the parathyroids might give some indication of the functional state of the gland.

Does this correspond with the views held by Paton, Findlay and Schafer? According to these authorities, guanidine should throw the parathyroids into greater activity, in order

that the excess of this substance may be further metabolised.

In R. 15, R. 16, and R. 13, the most striking change in the parathyroids was the disappearance of the larger globules. After 48 hours, the normal appearance returned, as seen in N. 314. The disappearance and reappearance of their large globules had a consistent relationship with the guanidine injections.

In short, up to 24 hours after an injection of guanidine, globules were relatively scarce in the parathyroids. At about 48 hours after an injection, the normal appearance had returned.

But what is the effect of repeated injections? The effect of the second dose was as marked as the first. R. 17 was killed 24 hours after the last injection. The appearance corresponds closely with that of R. 13. However, the later stages of recovery as seen in R. 18 were not so complete as when only one injection was given.

R. 18 was killed in 9 days—3 days after the last injection. The large globules were not at all rare, but in numbers they could not be compared with the picture seen in either N. 314 or R. 12. In R. 18, the small globules predominated. After 3 days, then, the glands had not recovered their normal appearance. There was still a suggestion of hyperactivity.

R. 14 received eight injections in 27 days. The seventh was given on the 25th day and the eighth on the 27th day. The animal was killed two hours after the last injection while in tetany. Latterly the animal was kept in a constant state of muscular hypertonicity. The resultant microscopic picture again showed the predominance of the small globules.

The chief point to be considered in R. 18 and R. 14 is the relationship the smaller globules bear with the activity of the cell. In R. 14, there was a pronounced hypertrophy of the parathyroid cells, and there were many indications of hyperplasia although no obvious mitosis was demonstrable. (Fig. 3.) It therefore seems to be highly probable that the small globules go hand in hand with an increased activity of the glandules. In other words, the cells had not sufficient time to accumulate their product in large enough quantities for the formation of the larger globules. In their place the smaller globules appeared.

It is also significant that only in R. 14 were the granular eosinophilic cells present in any appreciable numbers. MacCallum suggests that an increased eosinophilic granularity of the cells may be associated with increased activity.

Transitional forms were seen between this and the more prevalent type of cell.

It can therefore be concluded that the microscopic evidence supports the views of Paton, Findlay and Schafer on the relationship which exists between the parathyroids and guanidine.

#### SUMMARY

1. An injection of guanidine nitrate causes the depletion of the parathyroid globules within 18 hours.
2. The normal appearance is restored in 48 hours.
3. Repeated injections, sufficient to keep a constant degree of hypertonicity in the muscles, causes hypertrophy and hyperplasia of the parathyroid cells, as well as a marked increase in the acidophilic cells, and a marked absence of the large globules.
4. Guanidine injections, therefore, involve increased function of the parathyroids as shown by the absence of large globules, the presence of small globules, hypertrophied cells and numerous eosinophilic cells.

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## STUDIES IN ACROMEGALY II. HISTORICAL NOTE\*

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Owing to the protean nature of the disease acromegaly, the literature concerning it has grown extremely voluminous. Each one who had an opportunity to investigate the clinical picture or post-mortem findings in a personally observed case was apt to stress the outstanding features presented by his particular patient, with a resulting confusion of opinions regarding the nature and origin of this strange malady. There have thus grown up "schools" of opinion, each championed by some outstanding contributor whose numerous followers have all inserted their personal modifications to the original hypotheses.

It is not the aim of this present note to review the entire literature on the subject of acromegaly, but merely to touch upon those points which appear to be essential to our present conception of the disease. The paper therefore will serve merely as an introduction to certain studies concerning diabetes, metabolism, the rôle of other endocrine organs than the hypophysis, etc., which are to follow.

In 1886 appeared Marie's clinical description (14) of a new disease, based on two cases, to which he gave the name of "acromegaly." He laid the foundation for all subsequent clinical studies by his classical description of these patients, but he made no attempt at the time to ascribe the malady to any particular etiological factor. In addition to these two personally observed patients, Marie also called attention to five other examples obviously of the same condition which had appeared in the literature under a variety of designations. These had been reported by Sauscerotte-Noël (1772), Alibert (1822), and Friedreich (1868), who reported the cases of the famous "brothers Hagner," whom Marie later considered to be examples of osteo-

\*For the first of this series of reports, cf. Bailey, P., and Davidoff, L. M.: "Concerning the microscopic structure of the hypophysis cerebri in acromegaly." *Am. J. Path.*, 1925, 1, 185-207.

arthropathy, and by Henrot (1877). On Henrot's patient an autopsy had been done and a large pituitary tumor found.

The next year (1887) Minkowski (19) reported a case of his own which he recognized as similar to Marie's two patients. This patient was an outspoken example of the malady and suffered from outstanding local pressure symptoms in the form of severe headaches and bitemporal hemianopsia. In his paper Minkowski called attention to a case which had been reported two years before Marie's original paper by Fritzsche and Klebs (11), who appear to have been the first to suspect the possible relationship of the disorder, which they considered to be one of pathological gigantism, with the ductless glands. Having found at autopsy an enlargement of both the thymus and hypophysis, they favored the former as the causative agent, and ascribed the enlargement of the pituitary to the general overgrowth of the body. They explained the fact, that this enlargement exceeded the relative proportions of other parts, on the grounds of the greater blood supply to the hypophysial region.

Minkowski was led to differ from these views of Klebs, having recently been impressed, as he said, by a lecture given by Virchow (1887), on the resemblance of the histological structure of the thyroid and pituitary glands. He argued from this that, since myxoedema is related to changes in the thyroid gland and is accompanied by trophic changes in the skin and extremities, acromegaly must be related to disturbances of the hypophysis since this disease, too, is evidenced by trophic disturbances.

On this weak link the pituitary gland seems first to have become associated with the disease acromegaly, but the exact nature of the disturbance of the hypophysis was barely guessed at.

Marie himself, under whose influence a thesis by his pupil Souza-Leite (15) appeared in 1890, including a summary of all the cases in the literature to date, 38 in number, was far from certain that the malady was due to a primary disturbance of the pituitary gland. Writing with Marinesco (16) in 1891, he summed up their studies of his first autopsy on an acromegalic, with the impression that they were evidently dealing with a general nutritional disease affecting especially the connective tissue of the extremities and certain organs and mucous membranes. The reason for this distribution of pathological changes,

he thought, depended upon the particular condition of the circulation and nutrition of the extremities and an embryological predisposition. From this point of view, he continued, the pituitary lesion might be considered simply analogous to any of the others, except for the fact that it is, first, a constant lesion, and second, not simply an interstitial sclerosis, but a hyperplasia of the follicles as well. He discarded as untenable the hypothesis of Klebs, that the thymus is responsible for acromegaly, or that the malady is primarily of nervous origin in accordance with the views expressed by von Recklinghausen.

In those days the question of whether the pituitary body had any function at all was still far from settled, and Marie was impressed by the recent experiments of Rogowitsch (22) in which an hypertrophy of the gland was shown to follow extirpation of the thyroid. It was the opinion of Rogowitsch that the thyroid and pituitary served to counteract various toxins of the body, and Marie came to believe that failure of the pituitary to function might permit these toxins to result in the occurrence of acromegaly in certain individuals with a special predisposition for the disease. Even as late as 1911, in a personal communication to Dr. Cushing, he stated that:

"After having passed from one hypothesis to another, I find myself in no definite position regarding this question [hypo- or hyperpituitarism]. I wonder if the solution does not lie in a somewhat different direction. That is to say, that the important fact concerns itself less, perhaps, with the quantitative function of the hypophysis than with the modification and alterations of its secretions."

On the whole, however, Marie was apparently inclined, up to this time, to regard acromegaly as an under-function of the hypophysis, and it was this indeed which led Horsley and others to attempt pituitary extirpations in order, if possible, to reproduce the condition experimentally.

It had long before been pointed out by Virchow (1863) that the functioning pars-anterior cells showed under the microscope a distinct granulation of the protoplasm. In 1892 Massalongo (17), on an histological basis having found in a case of acromegaly a pituitary tumor consisting of granular cells, concluded that this malady was an expression of hyperfunction of the pituitary. He, too, in a manner similar to Fritzsche and Klebs, believed that the thymus was responsible for the overgrowth, but assigned to the pituitary an equal and possibly a greater

share in this disturbance. This was the first expression in the literature against the somewhat tacitly assumed attitude that acromegaly was a disturbance of diminished activity of the gland. In 1894 Tamburini (25) described a case of acromegaly with autopsy findings, and clearly called attention to the hypertrophy of the epithelial elements of the pituitary gland, more specifically the chromophile cells. He concluded that the pituitary lesion was in the nature of an adenoma, but was different from adenomas in other glands in that it seemed to involve the entire organ—an assumption which is not borne out in most cases by later studies of other investigators. In an effort to explain the bizarre lesions of the hypophysis, said to have been found in cases of acromegaly, such as sarcomas and gliomas in earlier reports, he believed that the disease began with an overactivity of the chromophile cells of the anterior lobe and that later this overactivity, with its anatomical counterpart of chromophile adenoma, gave way to the degenerative lesions described by others, and that these were associated with clinical manifestations of underactivity of the gland, manifestations which were, to be sure, extremely vaguely sensed in his time.

In 1895 Brissaud and Meige (2) elaborated the views already expressed by Massalongo on the relationship and similarity between acromegaly and gigantism. In 1897 Sternberg (23) wrote an excellent monograph, bringing together all the data available in the literature then extant on 210 reports of trustworthy examples of the disease, and 47 reports of autopsies.

The logic underlying the belief that eosinophilic granules appearing in the cells of acromegalie hypophyses necessarily mean hyperfunction was placed on a more reasonable basis by the special work of Benda in 1900 (1) in demonstrating, in addition to his excellent preparations with special stains for granules, the fact that in young individuals during their growing period the eosinophilic granules are much more common than in older individuals, granular cells often extending into the tuberalis, and this occurrence being less and less common as age advances.

This disclosure was promptly recognized as of great significance, particularly in that it offered an explanation for acromegaly on a pituitary basis, even in the absence of an hypophysial enlargement or tumor. In discussion of a paper by

Benda on the subject, Virchow (1900) (27) stated that pathologists could no longer be content to regard a pituitary gland in acromegaly as normal on its gross appearance alone, but that the special examination for granules would have to be carried out. He stated further that in his collection there were five typically acromegalic skeletons with normal pituitary fossae, a fact which could no longer be regarded as incompatible with overactivity of the gland.\*

Somewhat varied explanations of acromegaly have been advanced by others. In 1895 Campbell (5) considered the malady as a reversion to the anthropoid stage of development. Woods Hutchinson (1898) (12), one of the earliest American physicians to write about the disease, believed it to be a developmental disorder resulting in hypertrophy in those parts of the body corresponding to the areas of closure of the "ventral arches" of the embryo. Cagnetto in 1904 (3), on the basis of some clinical and pathological studies, expressed the view that it was not primarily a disease of hypophysial origin but that overgrowth and the hypophysial changes were both consequent to a general nutritional disorder. Accordingly, he was pleased to report in 1907 (4) a case of acromegaly which appeared to show at autopsy a pituitary tumor consisting entirely of chromophobe cells. He concluded that all that remained was for someone to find a chromophile adenoma without acromegaly, in order to complete the proof against the hypophysial origin of the disease.

In the same year (1907) Petrén (20) also expressed doubts as to the hypophysial origin of acromegaly, basing his opinion upon a personally observed case with a normal sized hypophysis and a coincidental syringomyelia. The latter finding led him to feel with von Recklinghausen (1890) (21) that the disease may be primarily of nervous origin. Indeed, also, in the same year, Magnus-Levy (13) wrote that: "neither pathological, experimental or clinical evidence exists to show with sufficient certainty that acromegaly is related to a change in the hypophysis, and assuming such a relation to exist, as most people believe,

\*This statement one finds hard to believe in view of the fact that in the Brigham Hospital series of 100 cases of acromegaly the X-ray has disclosed an outspoken enlargement of the sella in all but seven cases. On this percentage basis Virchow would have needed to have skeletons of 71 acromegalics in his collection.

whether this change is one in the direction of increase or decrease of function."

Owing to the frequent and often very early disturbances of gonadal function in acromegaly, Stumme (1908) (24), Thumm (1909) (26), Mayer (1910) (18) and others believed that the primary disorder lay in the sex glands, and that this resulted secondarily in those changes of the hypophysis said to be characteristic of acromegaly.

There had been one most confusing fact, namely, the occasional report of cases of acromegaly in which not only was the hypophysis not enlarged but was said to be histologically normal. Erdheim, however, in 1909 (8) cast doubt upon all case reports of this kind by the report of such a case in which he had found a large, apparently separate eosinophilic adenoma, within the sphenoidal cells, supposedly having originated from an anlage of the craniopharyngeal pouch. This case aroused great interest and led, if to nothing else, at least to more careful examinations of the base of the skull in subsequent autopsies.

In 1909 also, Cushing (6) in his address before the Surgical Section of the American Medical Association, first employed the terms hyperpituitarism and hypopituitarism, the latter having been used for the states of experimental pituitary insufficiency which he with Crowe and Homans had been the first to produce or at least to describe. Since these experimental states of adiposity and sexual dystrophy resembled certain unexplained clinical syndromes accompanied by hypophysial tumor, acromegaly was regarded as in all probability the counter-state due to over-glandular secretion or hyperpituitarism. Three years later in his monograph on the pituitary disorders (7) Cushing assembled the arguments for his own belief in the hyperpituitary nature of acromegaly in the following manner:

1. "In the first place, in the only known conditions associated with skeletal overgrowth one usually finds an hypertrophic enlargement of the gland or a histologically demonstrable hyperplasia—primary in the case of acromegaly and gigantism, secondary in the case of eunuchism.

2. "Moreover, experimental extirpations of the hypophysis, with resultant glandular deficiency, have been shown to retard skeletal growth, and comparable effects are known, clinically, to be the consequence of glandular implication in tumor, injuries, or processes of disease in young individuals.

3. "Again, acromegaly tends in the long run toward a state which our experiments have shown to be brought about by glandular

insufficiency—adiposity, high sugar tolerance, and so on—and the fact that a low assimilation limit for carbohydrates characterizes the early stages of the disease suggests a coincident period of functional hyperplasia.

4. "Further, partial removals of the presumably hyperplastic pars anterior in certain cases of advancing acromegaly have led to seeming remissions in the symptoms, in the same way that partial removals of the hyperplastic thyroid in Basedow's disease induce remissions in the symptoms of hyperthyroidism."

Clinical and anatomico-pathological studies have continued with varying degrees of intensity up to the present time, but with perhaps no more advance than was made in these earlier years when the subject was of more universal interest than at the present. Dr. Cushing recognized at the time of his monograph that the solution would probably come from the experimental laboratory. He says:

"Experimental investigations, as we have seen, have thrown merely a negative light on the matter in so far as they have made clear that hypophysial deficiency—presumably of pars anterior—inhibits complete skeletal development; and it has been suggested that this may be due to a consequent lowering of the phosphorus and calcium content of the blood.

"So far as I am aware, there is only one certain experimental method of inciting skeletal overgrowth, namely, by early castration, and it is probable, after all, that, as Tandler suggests, the skeletal elongation characterizing eunuchism is merely an expression of a secondary hypophysial hyperplasia.

"No one has definitely succeeded in simulating a fixed state of functional overactivity of any member of the ductless-gland series, whether by feeding-experiments or by heterogeneous transplantations.

"Unquestionably there is some chemical process at work behind the actual glandular hyperplasia (Vassale, Cagnetto, *et al.*), and until this can be determined we must not only await the experimental reproduction of states of functional overactivity but must also continue to speak of the glandular change as the primary incident in the process."

This experimental proof which he felt was necessary for the final demonstration of the hyperactivity of the pituitary in cases of acromegaly and gigantism has finally appeared through the efforts of H. M. Evans and his co-workers (9) (10) at the University of California, where at last it was demonstrated that by the parenteral injection of an extract of the anterior lobe of the pituitary gland true gigantism can be produced experimentally in rats. Obviously the hormone which influences growth resides in this portion of the gland, and there are ample reasons to believe it is a function of the acidophilic cells, which are those chiefly composing the adenomas of acromegaly as Benda first pointed out. It only remains for some-

one by similar methods to produce the experimental counterpart of acromegaly. For this, some animal of a species in which, unlike the rat, the epiphyseal growth of the bone ceases in the adult, will needs be employed.

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STUDIES IN ACROMEGALY  
III. THE ANAMNESIS AND SYMPTOMATOLOGY IN  
ONE HUNDRED CASES

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INTRODUCTION

This study is based upon an analysis of the 100 cases which were discharged from the Peter Bent Brigham Hospital with the diagnosis of acromegaly, up to August 1, 1926. Nearly five times this number of patients with pituitary tumors have been studied here since the hospital was opened in 1913, but the 100 cases chosen for this analysis are those in which the acromegaly was paramount and unmistakable. We have purposefully avoided the inclusion of mixed types or borderline cases of dyspituitarism in which traces of acromegaly were discernible on histological or X-ray studies but which have become submerged in hypopituitarism.

Fifty-six of these 100 cases were primarily admitted because of the pressure effects of the acromegalic adenoma against the chiasm, and were operated upon for the relief of these symptoms. Sixteen others had either early signs of chiasmal pressure insufficient to warrant operation at the time, or signs sufficiently advanced to justify intervention which for one reason or another was postponed. In the remaining 28 cases there were no perimetric evidences whatsoever of chiasmal involvement.

Our material has the advantage of having been subjected to the relatively uniform management of a single clinic under the supervision of a single observer and within a period during which some notable advances in the knowledge of these disorders have been made. Inasmuch as all the reports in the literature are based on only a few personal observations, or on the data collected from the literature, it is hoped that some more clearly-

cut generalities may be deduced from this large and favorably studied group of cases.

#### INCIDENCE

The bizarre appearance which acromegaly lends to its sufferers, the mystery of its origin, the presentiment of scientists that its elucidation might provide a key to many endocrine problems—these and other factors have contributed to stimulate much work upon this subject. Yet the disease is a rare one—far more uncommon than other forms of pituitary disorder. Even in this particular hospital where, owing to an especial interest in the condition, acromegalics are frequently found, there have been only these 100 outspoken examples of the disease out of 50,000 patients admitted during the 12½ years under review, whereas the records show nearly 500 cases of pituitary disease of all sorts. Naturally, this being a surgical clinic, most of these patients are admitted because of tumor manifestations aside from other disturbances, and the surgically verified cases also show that the hypophysial adenomas *without* acromegaly are about five times as frequent as those *with* acromegaly.

*Race.* All of the patients in this series were members of the white race. Dana (1893) (11) reported a case in a Bolivian Indian. Yamada (1917) (31) described a case in a Japanese who was also suffering from beriberi; but a normal hypophysis was found at autopsy, and the published photographs of the patient's lower extremities are not convincing. A thorough search of the literature reveals only four examples reported as occurring in negroes [Berkley (4), Lackey (18), Krumbhaar (17), and Rake (27)], no one of which is strikingly acromegalic. Lackey's patient was a giant 8 ft. 6 in. tall, but with extremities and features in keeping with his race and great size.

The distribution among nationalities in our 100 cases was as follows: Forty-four Americans (native-born with Anglo-Saxon names), 21 Jews, 8 English, 8 Irish, 3 Germans, 3 Scandinavians, 4 Italians, 2 French, 1 Spanish, 1 Syrian, 1 Belgian, 1 Portuguese, 1 Armenian, 1 Hungarian, 1 Greek. The presence of 21% of Jews among our 100 cases is striking, for this proportion is, of course, far in excess of the relative number

of Jews in the American population (*viz.* 3.4%).<sup>1</sup> Similar observations have been made in regard to other endocrine disorders. Thus Lorand (1903) (20) in discussing the well-recognized frequency of diabetes among Hebrews, adds that acromegaly is also frequently seen among them, and quotes Maximilian Sternberg to this same effect. One wonders consequently whether the more highly strung, nervous make-up so frequently observed in members of this race is not associated with some instability in the endocrine mechanism.

**Sex.** Of our 100 patients, 44 were males, and 56 females. This seems to be an unusual preponderance of females in comparison with the findings of other observers, who usually cite the number of males as slightly in excess of females. Arnold (2), for example, found the proportion of males to females to be 55% to 45% out of 56 cases that he collected from the literature. Boyd (5), who gathered statistics on 65 cases, found 52.4% of these to be males and 47.6% females. A calculation on all the available case reports in the literature, exclusive of our own, makes the proportion of males to females 52% to 48%. It is obvious then, that the disease is equally proportioned between the sexes.

**Age.** The average age at which our patients came into the clinic was slightly above 40 years. The male patients averaged 33, and the female 45 years. Acromegaly, being essentially a chronic disease, however, the age of admission to the hospital can of itself have no significance except as a measure, roughly, of this chronicity.

Of far greater importance is the age of onset of the disease, and this unfortunately, is difficult to ascertain, for how is a patient to tell, even in retrospect, when such an ailment first made its appearance? The best one can do is to take as a starting point the age at which the patient first noted the presence of any of the symptoms known to be associated with the disease. On this basis it was estimated that the average age at which the malady began was 26.9 years. The actual range of ages was between 14 and 51, but by far the larger number fell into the third decade of life. This coincides very closely with

<sup>1</sup>In the last census (1920) the total population in the United States is given as 105,710,614, and the number of Jews as 3,600,350.

the figures in the literature, although the patient of Schultze and Fischer (29) began to show distinct acromegalic changes at the age of 11, and died at 15, of a large intracranial extension of her pituitary tumor. Other reports of so-called "infantile acromegaly" are rare, and not too convincing. The calculated onset in decades in this series as compared with that found by Sternberg (1897) (30) in 55 male and 70 female patients from the literature, is as follows:

P. B. B. H. series:	Sternberg:
male and female	male and female

10 to 20 years of age.....	19%	14.4%
20 to 30 years of age.....	53%	52.0%
30 to 40 years of age.....	18%	25.6%
After 40 years of age.....	10%	8.0%

The disease, then, may be fairly stated to have its onset during the first half of adult life, and over 50% fall in the third decade.

*Occupation.* There was no undue proportion of individuals employed in what are known as the "dangerous industries." A slight preponderance existed of people engaged in professions or skilled trades.

#### FAMILY HISTORY

In four cases a definite history was obtained of acromegaly affecting a near relative (1 sister, 1 father, 1 uncle, 1 aunt). Twenty of the patients gave a history of having one or more near relatives who were either very noticeably large people, or had strikingly large hands, feet or features. This figure is conservative, for it includes only those cases in which the history definitely states that the matter was inquired into. Four patients had relatives who were abnormally fat. In two instances a member of the patient's family had diabetes, and one of the diabetics was insane. One patient had a father with progressive muscular atrophy; another patient, a woman, had a child much overgrown, apparently with pubertas praecox. A presumably negative family history with regard to acromegaly, or other endocrine or nervous disturbances existed in the anamneses of the remaining 68 patients.

The reports in the literature concerning this point are usually indefinite, but it is not uncommon to find accounts of acromegaly, gigantism or growth up to the maximum limits of normality, and of neuroses and psychoses affecting members of the patients' families.\* While far from leading one to conclude that acromegaly is a familial disease, the information at hand at least suggests that certain propensities in a given family may become sufficiently exaggerated in one or two families to give rise to this condition.

#### MARITAL HISTORY

Only 64 of the 100 patients were married at the time of admission to the hospital, in spite of an average age of 40 years. Of the 44 male patients 26, or 59%, were married; and of the 56 females 38, or 68%, were married. The slight discrepancy

TABLE I  
Effect of Acromegaly on Fecundity

	At time of admission	(average no. years married: 14.7)		
		Average no. pregnancies per marriage.	Average no. children per marriage.	Average no. miscarriages per marriage.
<b>MALES</b>				
14 males married 1-17 yrs. before the onset of symptoms.....	2.9	2.6		0.29
5 males married 1-7 yrs. after the onset of symptoms.....	1.4	1.2		0.2
5 males—relation of marriage to time of onset of symptoms unknown....	4.0	3.4		0.6
Total of 24 male patients with presumably healthy wives.....	2.8	2.5		0.33
<b>FEMALES</b>				
27 females married 1-20 years before onset of symptoms.....	2.0	1.05		0.48
9 females married 0-10 years after the onset of symptoms.....	1.1	0.88		0.22
Total of 36 females with presumably healthy husbands.....	1.8	1.38		0.41

\*Fraenkel, Stadelmann and Benda's (1901) (16) second patient had a father, brother and sister, all of whom also had acromegaly.

may be accounted for by the corresponding discrepancy in the average age of the female patients (45 years) when admitted to the clinic, as compared to that of the males (33 years). Naturally the factors of race, social and economic standing, all have their particular modifying effects. But the chief factor in so small a percentage of marriages is undoubtedly the disease itself. Very few patients in whom the disease is full-blown marry, partly, no doubt because of their disfigurement, but largely because of the early secondary disturbance in the gonads.

The effect of the disease on fecundity is shown in table I.

It will be seen from this table that the average number of children in the families of these patients, particularly those who married after the onset of symptoms, is considerably restricted, especially in the case of the female patients.\* Considering the marked disturbances in the sexual life of acromegalics—a point to be considered in detail later on—these facts could be readily anticipated.

#### PAST HISTORY

*Development.* Eighty-four patients gave a history of normal physical and mental development before the onset of the disease. Ten gave a history of excessive growth after the age of puberty (13-14 years). Two were said to have been noticeably backward mentally. Two patients reached maturity late in life (puberty at 20-22 years). Two patients were always small, weak and delicate before the first symptom arose.

*Previous Illnesses.* The incidence of serious diseases occurring at some time or another before the onset of the acromegaly did not seem greater among these patients than among persons generally of corresponding age. It may be noted that 26 of the patients had had antecedent operations: tonsillectomy 8, appendectomy 6, pelvic operations 5, etc.; also that 9 others gave a history of trauma—of the head in 6 instances; but none of these episodes appeared to be definitely associated in any instance with the onset of the acromegaly itself.

\*The number of children per marriage in the United States is dependent upon such a large number of factors that no absolute figures are available for comparison, although statisticians assume as a working basis three children per marriage as a normal average.

Earlier writers have attempted to ascribe the disease to a variety of illnesses from which the patient was suffering previous to, or at the time of its onset. In our own series the following infectious diseases were recorded: Fifteen cases of scarlet fever, 12 typhoid fever, 6 diphtheria, 4 pneumonia, 4 influenza, 4 malaria, 3 otitis media (one with mastoiditis), 2 pleurisy, 2 meningitis, 2 syphilis, 2 smallpox, 2 acute rheumatic fever, and one case of pulmonary tuberculosis. It is difficult to believe, however, that any of these recorded maladies have any active etiological bearing on the disorder. In the majority of cases, namely 58, the earliest symptoms set in with no apparent stimulus. In only 14 did the onset coincide sufficiently closely with some preceding incident to suggest any relationship whatsoever. These may be listed as follows: In 3 cases it followed typhoid fever; in 2 cases a blow on the head; in 2 cases miscarriage; in 3 cases pregnancy; in 1 case cessation of nursing; in 1 case scarlet fever; in 1 case syphilis; in 1 case pleurisy with effusion.

In these few instances the patient had been in good health until the particular happening which supposedly was precursor to the endocrine disorder. In illustration, one patient was a Russian Jewess who was married, had borne two children, and enjoyed apparently perfect health until 29 years of age. Then, after a long siege of typhoid her menses became scanty and finally ceased. She remained weak and apathetic, gained weight gradually, and began to suffer from occasional frontal and sub-occipital headaches, which progressively became more severe. Ere long the clumsy appearance of her hands and feet was called to her attention by her friends.

The literature contains many examples of this same sort, but it may be pointed out that in only three of the 12 patients in the series who had typhoid did the fever appear to closely precede the pituitary derangement. It is nevertheless of interest to speculate on the possible connection between infections and growth which seems to be especially active during the course

of typhoid fever. In exceptional instances this amounts to two or more inches of added height in a few weeks.\* Rheumatic fever, syphilis, pleurisy and injuries, especially to the head, have also been frequently mentioned as causative agents. Even fright has been recorded as an etiological factor, as in Pel's (26) much-quoted case. Indeed, the variety of conditions, following which the symptoms of acromegaly may first appear, is evidence of the fact that no known disorder stands to the condition in the relation of cause and effect.

#### THE DISEASE ITSELF

*Symptoms.* The distinction between subjective and objective findings in acromegaly is particularly difficult to draw, for so many symptoms of the disorder belong to both categories; and it is not unlikely that many of the patients may have suffered from vague ill-health and have undergone profound changes in personal appearance, obvious to all others than themselves, before they recognized their disfigurement. That this might happen even in the case of a physician is recorded in Dr. Leonard Mark's autobiography of an acromegalic (22). The author had been a victim of the disease for many years before he accidentally discovered the nature of his malady. His friends, medical and otherwise, had meanwhile refrained from mentioning the subject, regarding his silence as evidence of sensitiveness, for they naturally thought he was aware of his condition.

The patients in this series appear for the most part to have had less considerate friends. Even so, a certain allowance must be made not only for the lapse of time between the actual onset of the disease and the recognition of certain symptoms, but also for the complete failure to recognize others that are less troublesome and less conspicuous. With these facts in mind, the symptoms and signs as recorded in the clinical histories have been assembled and are presented in table II in the order of their diminishing frequency.

\*Cf. "The Pituitary Body and its Disorders," pp. 236-237.

TABLE II

Symptoms and Signs of Acromegaly as Recorded in Clinical Histories

SYMPTOM	INCIDENCE
Enlargement of acral parts.....	100%
Enlargement of sella turcica on X-ray examination.....	93
Disturbances of menstrual cycle.....	87*
Headaches .....	87
Complete amenorrhoea .....	78†
Increased basal metabolic rate.....	70‡
Visual disturbances .....	62
Excessive perspiration .....	60
Hypertrichosis .....	53
Cutaneous pigmentation .....	46
Drowsiness and lethargy.....	42
Gain in weight.....	39
Diminished libido sexualis.....	38
Asthenia .....	33
Low blood-pressure (less than 120 mm. Hg. systolic).....	30
Paraesthesia .....	30
Polyphagia .....	28
Fibromata mollusca of skin.....	27
Polydipsia .....	25
Enlarged thyroid gland.....	25
Glycosuria (diabetes mellitus 12).....	25
Constipation .....	20
Vomiting .....	16
Rhinorrhoea .....	15
Photophobia .....	12
Uncinate attacks .....	7
Failing memory .....	7
Decrease of body hair.....	7
Persistent lactation .....	4
Failure of breasts to develop.....	4
Epistaxis .....	3
Choked discs .....	3

This formidable list of symptoms, especially when it is remembered that most of the less obvious ones actually occurred many times more often than would appear from the patients' own observation, indicates the far-reaching hold that acromegaly has upon the entire constitution of its victims. Unfortunately the pathological changes underlying many of these symptoms are obscure or quite unknown, but it is hoped that by reviewing them analytically, at least a tentative conception may be gained of the mechanism which results in this disease.

*Acral Overgrowth.* The typical and well-known changes in the features and extremities is of necessity present in all the cases, since not only the name but the clinical diagnosis of the disease, has, in the past at least, been based upon these

\*Percentage of female patients.

†Percentage of female patients.

‡Percentage of 70 cases examined.

peculiarly localized manifestations of overgrowth. That this overgrowth, which as a matter of fact is a general and not a local process confined to the extremities, is related to a disturbance of the hypophysis can no longer be questioned; for although the many physiological activities of the gland remain imperfectly understood there is abundant evidence to prove that it is intimately related to the processes of growth. There is, in the first place, the negative evidence, brought out particularly by Fichera (1905) (15), Aschner (1909) (3), and others, that experimental hypophysectomy results in the stunting of growth. Then there exist numerous points of indirect evidence such as the enlargement of the pituitary in giants, and in castrated individuals that have grown beyond the usual size of their species. Moreover, it had long been observed that acromegalics whose disease began before the age at which closure of the epiphyses normally occurs were apt to be of particularly large stature. Brissaud and Meige (6), and others have gone so far as to say that acromegaly and gigantism were one and the same disease, the apparent difference depending entirely upon the age of onset.

The average height of our male patients whose disease began before 20 years of age was 6 ft. 2 in. (186 cm.), and the average height of the women in whom the same age relationship occurred was 5 ft. 6½ in. (166.25 cm.). The explanation of the continued growth even after the normal age for the cessation of this function has been ascribed by Dr. Cushing to the failure of the epiphyseal lines to close in these individuals.\* Finally, H. M. Evans and his co-workers (13) (14) have succeeded in experimentally producing gigantism in rats, a species in which epiphyseal growth persists throughout life, by the injection of fresh anterior-lobe substance. Though the peculiar disposition of overgrowth in acromegaly has not been experimentally reproduced as yet, it may nevertheless be ascribed with full assurance also to a hyperfunction of the anterior lobe.

*Disturbances of the Menstrual Cycle.* As may be noted from table II, in 49 (87%) of the 56 female patients there existed a disturbance of the menstrual cycle amounting usually (in 73%) to a complete amenorrhoea by the time they first came

\* Cf. the case of the giant, Turner, Case XXXII in "The Pituitary Body and its Disorders."

under observation. The early menstrual history seems for the most part to have been devoid of incident; the average age of onset of menstruation was 14 years. But the cessation of the menstrual cycle in the 41 patients in whom this had taken place occurred at an average age of only 31.4 years, with a distribution in decades as follows:

- Before 20 years 3 patients ceased menstruating.
- 20 to 30 years 17 patients ceased menstruating.
- 30 to 40 years 10 patients ceased menstruating.
- 40 to 50 years 7 patients ceased menstruating.

Thus we see taking place in the female patients a pathological amenorrhoea at an age nearly 20 years younger than the average normal time of menopause which the recent studies of Dickinson and Pierson (12) put at 49 years.

The effect on the menstrual cycle may be presumed to be not simply an interruption of the local phasic changes in the uterus, but of the controlling ovarian function as well, for in none of our cases—and this is also true of studies by others—has any woman with acromegaly become pregnant in the presence of partial or complete amenorrhoea. It is also of importance to note in this connection that in six of our patients the disease dated from the time of pregnancy, after which catamenia never became re-established.

On the other hand, 13% of our female patients continued to menstruate quite regularly in spite of advancing acromegaly; one or two of them even bore children. We have one case (Surg. No. 4465) whose disease began at the age of 27 with amenorrhoea. At 31 she was operated on by Dr. Cushing, who partially extirpated an eosinophilic adenoma of the pituitary by a transphenoidal operation. Her vision improved and her headaches ceased. Four years after her operation she began to have profuse uterine bleeding. The cause of hemorrhage was discovered to be a cervical polyp, which was removed by operation, and following this operation, after 8 years of amenorrhoea, regular periods were re-established.

The frequency of premature cessation of menstruation occurring, as will be shown later on, so early in the disease, would at first sight appear to be incompatible with the conception of

pituitary hyperactivity, for it is well known that in another and far more common type of pituitary disorder termed hypopituitarism, which is taken to be the exact antithesis of acromegaly though also due to an adenoma of the gland, amenorrhoea is an even more constant early symptom.

But here again the experiments of Evans and his associates have thrown light on the subject. Their injections into female rats of anterior-lobe pituitary substance were originally made for the sake of studying the effects upon the oestrous cycle, and it was soon discovered that the hypophysial extract very promptly interrupted this cycle. Later, however, in examining the ovaries of animals so treated, instead of finding shrunken, fibrosed organs, the ovaries were found to be actually larger than normal ones, and owing to their irregular surfaces were termed "mulberry ovaries." On microscopic examination these irregularities proved to be corpora lutea, each containing an undischarged and degenerated ovum.

Unfortunately there is no record of a satisfactory examination of the ovaries of a female acromegalic who was sufficiently young to have disclosed a condition—if indeed such a condition exists—analogous to the mulberry ovary produced in Evans' experimental animals. In any case, the frequent and early cessation of the menstrual cycle in acromegaly is so comparable to a similar effect produced upon the oestrous cycle of the rat by an excessive supply of anterior-lobe substance that a similar cause may certainly be assumed to be at work.

*Headache.* The headache in acromegalic patients may be due to factors additional to that of increased pressure within the pituitary capsule, for among our cases there have been some who were entirely free from headache and who nevertheless showed a very large sella turcica, and others whose chief complaint was headache, sometimes most persistent and excruciating in nature, and yet by X-ray examination proved to have a small, or relatively small, sella. Indeed in one case with extremely severe headaches an autopsy showed a pituitary of practically normal size. However, the fact that out of the 13 patients in the series who were free from headaches 9 showed no visual-field defects, would seem to support the view that headache is probably due in the majority of cases to the intra-

capsular pressure from the enlarging gland. This at least appears to be true of the cephalgia in patients with hypophysial adenomas unassociated with acromegaly, for by the time the sella has become fully ballooned the discomforts usually cease.

In this connection it may be pointed out that only 7 of the 100 cases showed sellar outlines which in profile could be considered to be of normal dimensions; all the others showed varying grades of sellar enlargement in spite of the fact mentioned above, that 28 of them were not operated upon because of the absence of demonstrable perimetric defects in the visual fields.

*Visual Disturbances.* These, as described in detail by previous observers from this clinic (10) consist usually of symmetrically disposed defects in the fields which progress downward until the typical bitemporal hemianopsia or even a more advanced stage of the process is produced. The cause of these changes is obviously due to upward pressure against the chiasm of the extending gland, which may ultimately rupture the capsule with marked intracranial extension of the lesion. This intracranial extension at times may pass through the capsule to one side rather than in the midline, and two of the cases in the series showed a homonymous rather than a bitemporal hemianopsia. Such a lateral expansion of the intracranial process naturally enough may lead to pressure upon and irritation of the uncus and produce the uncinate attacks, which, as mentioned in the table, were recorded in seven cases.

Needless to say, these disturbances of vision are accompanied by a primary optic atrophy which may go on to produce complete blindness. Rarely does a choked disc occur. In only one case in the series was it marked, though in two others a slight papilloedema was recorded. In all these instances there was evidence of marked intracranial extension of the process leading to general pressure symptoms, with vomiting and so on, such as one may see in a larger percentage of patients with chromophobe adenomas associated, from the onset, with pituitary insufficiency and without any trace of acromegaly.

Summarily then, in addition to the disturbances in the glandular activity of the pituitary which occurs in all cases of acromegaly, an enlargement of the gland took place in 93% of this series. This enlargement was accompanied at times by

headaches alone, at others only by visual-field defects, but in the majority of cases by both. With all due emphasis, however, on these symptoms attributable to local pressure, it must be borne in mind that outspoken acromegaly may occur in the absence of any clinical evidence of a demonstrable enlargement of the hypophysis.

*Drowsiness and Lethargy.* These are difficult symptoms to estimate. They are much more common in cases of pituitary insufficiency, yet strangely enough occurred in 42% of these acromegalics, and were often marked, in spite of advanced hyperpituitarism. In a few of these patients, the presence of an intracranial extension of the tumor may have been responsible, but in the greater majority these peculiar complaints remain for the present unexplained.

*Cutaneous Manifestations.* Among these may be considered the symptoms which have been tabulated under hypertrichosis, excessive perspiration, cutaneous pigmentation, fibromata mollusca, loss of hair, and so on. It is safe to say that many of these may be ascribed to the hypophysial derangement and may well enough represent the hypertrophic changes of the cutaneous appendages. The hypertrichosis, for example, is often striking. The hair of the scalp, pubes and axillae is not especially affected in quantity, but the remainder of the body becomes extremely hairy, even in women, who often tend to develop beards. But even more noteworthy than the amount and distribution, is the quality of the hair, which is thick, wiry and oily. Moreover, it has its reverse picture in the delicate, fine, silky hair of the head, and comparative hairlessness of the body, in persons the victims of pituitary insufficiency from adenoma or other causes.

In the same way the enlarged sebaceous and sudoriferous glands may account for the excessive sweating and oiliness of the skin, and thus for the peculiar disagreeable odor which frequently surrounds acromegalics. Although proof of this hypertrophy exists by microscopic examination, it is hardly necessary, for the large widely open pores visible on inspection of the skin of one of these patients appears like an equal area of normal skin viewed through a magnifying glass. The dry, soft,

thin, delicate skin characteristic of patients with hypopituitarism is again confirmatory by contrast.

In 27 cases the presence of fibromata mollusea was mentioned, and one or two of the patients have been sufficiently annoyed by these cutaneous tags to have some of them surgically removed. Histologically, of course, these, too, are but an expression of local hypertrophy of subcutaneous fibrous tissue.

In a few other patients there have been small subcutaneous lipomata, and in one patient a large lipoma of the back. What bearing this may have, if any, on adiposity, is not clear. There are frequent statements made in the histories, regarding ravenous appetites, and the early gain in weight is undoubtedly due largely to increase in massiveness of the body, but certain of these people later on become distinctly adipose and give the impression of losing some of their acromegaly and suggest more the picture of cases of pituitary insufficiency, though of course the bony changes once established are never lost. The occasional transition from hyperactivity to insufficiency of the pituitary gland may also account for the seven patients who were found to have a distinct decrease of body hair.

Brown pigmentation of the skin occurred in 46 patients; the significance of this also must remain essentially unexplained. But the presence of asthenia in 3 cases and a distinctly subnormal blood pressure in about an equal number would suggest some interference with adrenal activity.

The pain, tingling and numbness of the extremities that we have grouped under "paraesthesia" are again but poorly understood except that they probably have some relation to the pituitary hyperactivity, for these symptoms have been observed frequently to disappear immediately after operation. The attempt occasionally met with in the literature to interpret the paraesthesia to a pinching of the nerve trunks by the hyperostoses surrounding the intervertebral foramina, is untenable, not only because of the improvement shown immediately after operation which cannot affect the hyperostoses so quickly, but also because one patient, whose skeleton has been preserved here, and which shows most extensive hyperostoses of the entire osseous system, never complained of paraesthesia. On the other hand, the hypertrophy of the lamellar sheaths with actual de-

generation of the nerve endings first described by Marie and Marinesco (24) may very readily be, in part at least, responsible for this type of discomfort.

*Polyglandular Disturbance.* There remain certain of the recorded signs and symptoms which may, for lack of better grouping, be brought together under this heading. The association has been touched upon above, in hinting at the possible relation of the pigmentation and asthenia to an adrenal participation. It is the opinion of this clinic that of all the ductless gland disorders, acromegaly (hyperpituitarism) shows grossly a more widespread involvement of the other endocrine glands than is true of any other primary derangement of one member of the series. A palpable or definitely enlarged thyroid, for example, was recorded in 25% of the patients. In one or two of them the goitre was so large as to cause dyspnoea and necessitate operation. In three cases hyperthyroidism was suspected and a subtotal thyroidectomy performed, the gland in each case proving to be merely of a colloidal type. Glycosuria was recorded in 25%; and the inevitable disturbance of the function of the sex glands has already been dealt with.

Just what may be the relation of acromegalic diabetes to true pancreatic diabetes, and the changes in the thyroid to the alterations in the basal metabolic rate (9) is not as yet determined. Though these matters will be more fully considered in subsequent papers in this series, certain facts in relation to them may be here briefly set down. The first concerns the question of:

*Metabolism.* It may be stated in brief that in patients with acromegaly the basal metabolic rate is usually above normal and sometimes markedly above normal, whereas in patients with the more common chromophobe type of pituitary adenoma unassociated with acromegaly it is almost inevitably subnormal. Of the 73 patients in whom the rate was tested 50 were above normal, the highest recorded rate being +61%. In 23 cases it was below normal, the lowest being -17%. These figures are in marked contrast to those in patients with pituitary lesions unassociated with acromegaly in which registrations of -30% to -40% are common. The acromegalics with enlarged thyroids that happened to have their metabolism studied proved

to fall into the group with rates registering above zero. Studies of this subject which will be detailed elsewhere show, nevertheless, that the hypophysis is primarily responsible for the disturbance of metabolism.

*Glycosuria and Carbohydrate Tolerance.* Twenty-five patients gave a history, or proved on examination of the urine, to have glycosuria. Of these, 12 had definite clinical diabetes mellitus, the others only a transient glycosuria. Fasting blood-sugar determinations, moreover, in a dozen other members of the series without glycosuria showed the sugar percentage to vary between 0.11%-0.16%; that is, approaching the upper limits of normal. This relatively large number of acromegalics showing sugar in the urine, and the fact that out of five times as many patients with hypopituitarism in the records of this hospital, only two or three showed glycosuria, makes it evident that this tendency toward decreased tolerance for sugar is not a mere coincidence.

The general subject of the carbohydrate metabolism as affected by acromegaly will be taken up in another communication. Suffice it to say that even evident clinical diabetes mellitus in patients also suffering from acromegaly frequently behaves in unexpected ways. Some data exist in our records, moreover, showing that reduction in hypophysial activity, as by partial removal of the pituitary tumor, results in an improved tolerance for sugar, thus suggesting that directly or indirectly hypopituitarism favors diabetes.

*Further Symptoms.* Persistent lactation over a period of years occurred in four female patients. It consisted in the presence of small quantities of yellowish fluid resembling colostrum evident on compression of one breast in three of the patients and both breasts in the fourth.

Brown (1925) (7) refers to a woman with "pituitary tumor" (presumably acromegalic) who had been lactating continuously for seven years. Roth (1918) (28) reports a case of acromegaly in a male patient in whom a secretion from the left breast became established which microscopically and clinically proved to be milk. A woman seen in the Brigham clinic, since the 100 cases forming this study were assembled, has been lactating without interruption for five years following a second

pregnancy, since when her acromegaly became manifest, and menstruation has not been resumed.

The studies of Miss Lane-Claypon and Starling proving the stimulating effect upon lactation of foetal tissue juices is evidently insufficient to explain the acceleration of mammary development and lactation in every case. Ancel and Bouin (1909) (1) have shown in their experiments upon rabbits that the stimulus in this animal at least arises from the corpus luteum, whether that of pregnancy or "pseudo-pregnancy." Leo Loeb (1917) (19) has proved this to be the case in guinea-pigs and has shown that when the entire ovaries or the corpora lutea alone are removed during pregnancy in this animal the mammary tissue fails to proliferate even though the pregnancy continues uninterruptedly to term. All this suggests that mulberry ovaries with persistent corpora lutea such as Evans sees in his giant rats may conceivably occur in some amenorrhoeic acromegalics and stimulate the secretion of milk.

The part played by the posterior lobe on milk secretion is believed by Sharpey-Schafer to be simply a stimulus to the smooth muscle-fibres of the mammary ducts. So far as the anterior lobe is concerned, Marshall (1922) (25) states that lactation may be prolonged for an almost indefinite period after ovariectomy, which as is known causes a secondary hypertrophy of the pituitary body. Hence he believes it to be not unlikely "that these two facts are correlated, and that after the removal of the ovaries the function of the corpus luteum in relation to milk secretion may be taken over vicariously by the pituitary." In the case of acromegaly mentioned above as having been too recently admitted to the hospital to be included in this series, in which lactation and amenorrhoea have persisted for five years, a report from a surgeon who had occasion to observe and to incise her ovaries during an abdominal operation, two years ago, states that "both ovaries were in a state of semi-atrophy without signs of ovulation."

The physiology of lactation even in normal individuals is evidently so poorly understood that an effort to explain it under these already complicated circumstances cannot be more than speculative. More readily comprehensible is the failure of the breasts to develop. This occurred in four young women whose

disease began at puberty and whose ovaries must, therefore, have become involved too soon to exert their influence upon the development of these secondary sex-characters.

Three patients, all of them female, had occasional free epistaxis, but in only one did this occur sufficiently periodically to have been regarded in the light of vicarious menstruation.

#### CHRONOLOGY OF SYMPTOMS

With complete understanding of the uncertainty attached to the treatment of data obtained from the anamnesis, we have nevertheless attempted to formulate a table of symptoms in the chronological order of their appearance, hoping that the preceding analysis of the symptoms and their origins may help us to follow the course of the disease.

TABLE III  
Time of Appearance of Symptoms

SYMPTOMS.	Average duration in yrs. at time of admission	Percentage of cases where it appeared as one of the initial symptoms	Percentage of incidence
Gigantic stature (6 ft [180 cm.] or over)	14.7	10.0	14.0
Irregular menses	10.5	26.8 (% of female patients)	42.8 (% of female patients)
Gain in weight	9.3	20.0	39.0
Increase in size of hands and feet	8.4	48.0	100.0
Coarseness of features	7.0	37.0	100.0
Complete amenorrhoea	6.4	26.8 (% of female patients)	73.0 (% of female patients)
Increased body-hair	6.3	7.0	53.0
Paraesthesia	5.7	11.0	30.0
Headaches	5.5	27.0	87.0
Drowsiness	4.9	6.0	42.0
Failing vision	4.1	10.0	68.0
Polyphagia	4.1	1.0	28.0
Excessive perspiration	3.7	3.0	60.0
Asthenia	3.6	5.0	33.0
Polydipsia,	3.4	2.0	25.0
Diminished libido sexualis (male patients).	3.0	4.0	38.0

In table III are presented in as nearly a summary fashion as possible what seem to be almost constant features of the *onset of the disease*, as case after case is studied in the present series, and in the literature wherever complete data is presented, namely.

1. An early period during which growth becomes accentuated, always expressed in an increase in the size of the acral parts and usually also of the entire body, especially the bony framework, sometimes amounting to actual gigantism, which is naturally accompanied by a gain in weight. This period is also characterized in the women by irregularity of the menstrual cycle or complete amenorrhoea.

These symptoms we have already seen in all likelihood associated with overactivity of the *pars anterior* of the pituitary gland. They are the most constant symptoms and are in the majority of cases the first manifestations of the disease, which may, therefore, be fairly assumed to begin with a hyperactivity of the gland.

2. Then follows a second period characterized by neighborhood symptoms resulting from pressure of the enlarging adenoma which occurs, in those cases where it is present, on the average of not until 3 to 6 years after the onset of the disease. In our patients, for example, 68 were suffering from failing vision at the time of admission to the hospital, but only 10% gave this as one of the earliest manifestations of their difficulties, and even in these 10% it is not inconceivable that a gradual increase in the size of the extremities may have gone unnoticed while the very first evidence of failing sight would, as a rule, have aroused the patient's apprehension immediately, and the time of its appearance be clearly recalled.

As noted beforehand, tumor symptoms are, subjectively at least, absent in a fair proportion (28%) of these cases, although the X-ray may usually (93%) detect an increase in size of the sella. It is true, nevertheless, that symptoms of hyperactivity very frequently begin before any evidence of pituitary enlargement exists, and may indeed run its course to full-blown acromegaly without any signs of tumor ever appearing on clinical or even X-ray evidence.

3. There is a final or third period when patients ordinarily first come under observation in which they show a con-

glomeration of secondary symptoms and signs indicative of the more far-reaching effects of the disorder ascribable partly to the late effects of visceral splanchnomegaly (cardiac in particular) and partly to a secondary effect of the other endocrine organs. Such evidence as glycosuria, to be sure, naturally remains unobserved by the patient and is, therefore, not discovered until clinical examination reveals it. On the other hand, the relatively late appearance of symptoms like polyphagia with especial appetite for sweets, polyuria, and polydipsia, would suggest a correspondingly delayed involvement of the glycolytic function of the body.

Thus we may say that acromegaly is a disease which begins with hyperactivity of the pars anterior of the hypophysis, which usually enlarges and forms a tumor, and as the disease advances other organs, but primarily the endocrine system, become involved in the disease.

#### SUMMARY AND CONCLUSIONS

An analysis of 100 consecutive cases of acromegaly observed at the Peter Bent Brigham Hospital during the years 1913-1926 has been undertaken, chiefly from the standpoint of the anamnesis.

Only two out of every 1,000 patients admitted to the hospital, and approximately one in every five with a diagnosis of pituitary disorder, presented this condition.

All the patients belonged to the white race. Twenty-one per cent were Jewish.

The relative incidence between the sexes is probably about equal.

The disease begins most commonly between the ages of 18 and 35 years, with an average age of onset of 26.9 years.

Certainly hereditary influences exist as shown by the fact that a family history of acromegaly in 4% of the cases, and in 20% a family history of noticeably large individuals was recorded.

The fecundity of the patients was below the usual average, and the number of children born to those who married after the onset of symptoms was small.

The anamnesis revealed no unusual susceptibility to any group of diseases or to any particular type of accidents. In the women the catamenia became established at an average age of 14 years, but cessation of menstruation occurred at an average age of only 31.3 years.

A very large number of symptoms were recorded, pointing to the far-reaching effects of this disease. The more important of these symptoms have been especially considered in their relationship to the seat of the underlying pathological changes.

From all this it would seem that the part played by the *pars anterior* of the hypophysis is undeniably one of primary importance. Its exact rôle is not yet entirely clear, but the hypertrophic changes so characteristic of the disease, occurring as they do in people at least half of whom have reached a maximal or even excessive stature before the apparent onset of the malady, are thought to signify a pathological hyperfunction of this gland which not only initiates the process but continues perhaps with varying intensity, throughout the course of the illness.

Usually the overactivity of the gland is followed by a tumor formation giving rise to pressure symptoms such as headache, bitemporal hemianopsia, and primary optic atrophy.

Finally other symptoms develop, which are obviously of a secondary nature. They are associated with a general splanchnomegaly with a profound disturbance of the reproductive glands, and with evidence of secondary involvement of other of the endocrine organs.

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# DEPRESSOR EFFECT OF TISSUE EXTRACTS THE DEPRESSOR EFFECT OF CERTAIN TISSUE EXTRACTS

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In 1896 Schäfer and Moore (1) while investigating the contractility of the spleen, noted that a fall of blood pressure usually followed the injection of brain extracts, and in 1899 Mott and Halliburton (2) suggested that the active substance was choline.

Osborne and Vincent (3) showed in 1900 that extracts of nervous tissues cause a fall in blood pressure, which is obtained after section of both vagi and after full doses of atropine. On the same date there appeared a communication by Halliburton (4) in which similar results were announced, but with the important difference that neither nervous tissue extracts nor choline produce a fall after atropine.

Vincent and Sheen (5) in 1903 showed that the depressor effect is obtained after injection of extracts of all tissues except the chromaphil. They found that, as in the case of nervous tissue extracts, extracts of other organs contain some depressor substance which is not choline.

In regard to the posterior lobe of the pituitary body, it was found by Schäfer and Vincent (10) that a depressor substance is present. A depressor effect is always obtained as a result of a second dose, the pressor effect being then absent. This depressor effect is not abolished by atropine, as that of choline is. Therefore the depressor effect of posterior lobe of pituitary is not due to the presence of choline. It was also shown by Schäfer and Vincent that the depressor substance is contained in the alcohol extract and can be removed by thorough extraction with alcohol. Recently Sharpey-Schafer and Macdonald (11) have shown that the substance in question is histamine, and the same view is expressed by Sharpey-Schafer in

his book on the Endocrine Organs, published in 1926 (Second Edition).

Few attempts to isolate the active principle or principles have been made. In 1903 Vincent and Cramer (6) isolated from nervous tissue extracts a substance which seemed to be a dicholine anhydride, while more recently, in 1926, Dale and his co-workers (7) after tedious and complicated processes have isolated histamine from ox liver. Although Dale's work tends to support the theory that tissue extracts owe their depressor activity to their histamine and choline content, certain results we have obtained indicate that other factors are involved as well. A preliminary communication was made in the *Lancet* by us on this subject (12).

#### PREPARATION OF EXTRACTS

The extracts employed were made from the tissues of cats, rabbits, and occasionally of guinea-pigs.

##### 1. *Saline Decoction.*

A weighed quantity of fresh moist tissue was ground in a mortar with sand, five times as many cubic centimetres of 0.9% normal saline solution being added as there were grammes of moist tissue; after thorough trituration the mixture was boiled with the addition of a few drops of dilute acetic acid. It was then filtered and the filtrate, after cooling, and refiltering if necessary, used for injection. In addition, portions of saline extracts were subjected to Pasteur-Chamberland filtration and further portions to shaking with benzene, as recommended by Pickering for removal of phosphatides.

##### 2. *Alcoholic Extract.*

The fresh moist tissue was pounded in a mortar with absolute alcohol and sand and left in contact with alcohol for some hours. The mixture was then filtered, the filtrate evaporated to dryness, and the residue taken up with 0.9% saline, five times as many cubic centimetres of saline being used as there were originally grammes of tissue. The fluid was again filtered and used.

##### 3. *Ether-Extract.*

This was prepared in a way similar to that for the alcoholic extract, except that methylated ether was used instead of alcohol as the extracting agent.

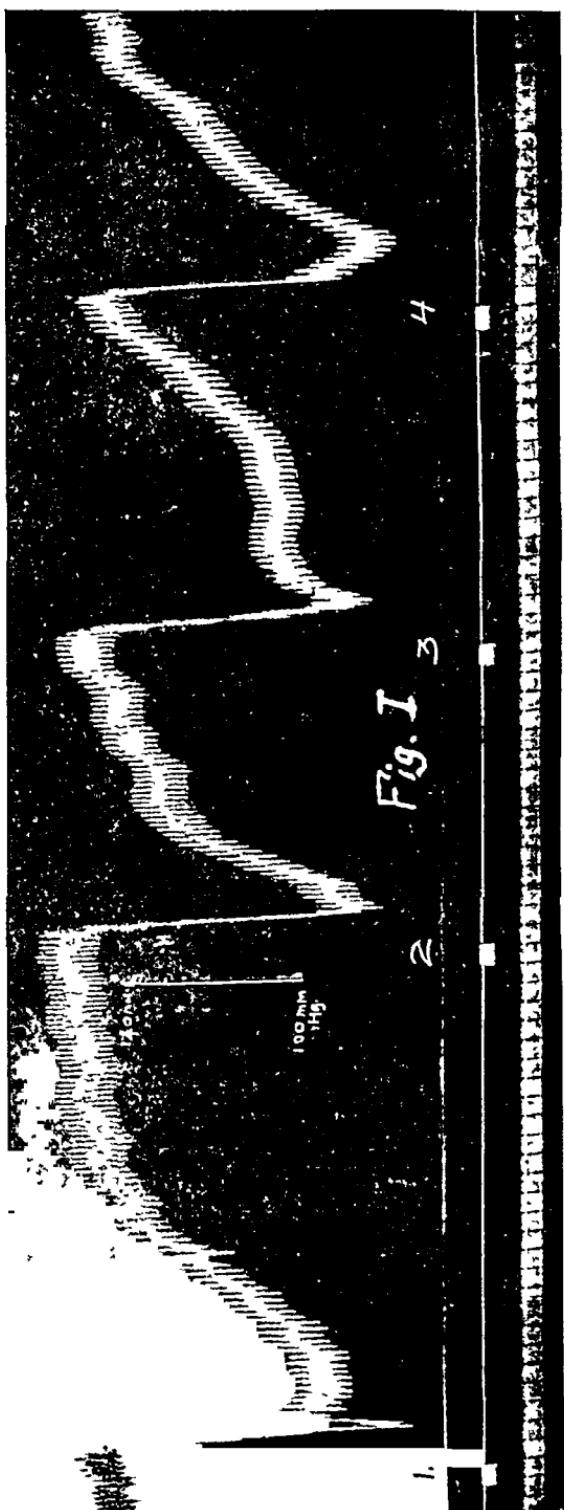


Fig. 1—Cat Ether. Time in seconds and ten seconds (1) 10cc saline extract of muscle (2) 10cc saline extract of lung (3) 10cc saline extract of liver (4) 10cc histamine choline solution (0.1 mgm an.).

#### 4. *Alcohol-Ether Extract.*

This was prepared by subjecting the residue after evaporation of the alcohol to the action of ether, then evaporating the ether after filtration, and taking up with saline as above. Solutions were prepared containing 0.01 mgr. of both histamine and choline in 10 c.c. of saline, and also solutions of 10 times the strength.

#### *Methods.*

Cats and rabbits were employed for the experiments. Anaesthesia was induced and maintained by ether.

The blood pressure was recorded from the carotid artery in the usual way by a mercury manometer. The vein used for injection was either the external jugular or the femoral.

The injections were made at room temperature, in 10 c.c. doses, which were given at the rate of 1 c.c. per second.

#### PHYSIOLOGICAL EFFECTS

Comparison of saline extracts and histamine-choline mixtures:

##### A. *In Cats.*

A striking resemblance is found between the curves produced by the injection of tissue extracts and histamine-choline solutions. In all cases there is a sudden fall with a more or less prolonged recovery. Results such as shown in Fig. 1 make it tempting to put forward the suggestion that tissue extracts owe their depressor effect to a mixture of histamine and choline.

##### B. *In Rabbits.*

Dale and Laidlaw (8) in 1910 showed that rabbits are peculiar in their reaction to histamine. If they are anaesthetized sufficiently to paralyze the bronchial muscles, histamine produces only a rise of blood pressure even in doses which would induce profound, even fatal, shock in a cat. Short of this stage of anaesthesia, considerable doses of histamine produce pulmonary constriction and usually a fatal spasm of the bronchial muscles which offers great obstruction to the entry of air. Dale and Laidlaw used urethane, but in our experiments it was found that 30-45 minutes of ether anaesthesia gave a condition in which histamine produces a rise of blood pressure.

It is obvious then that we have in the rabbit a most suitable animal for investigating the effect of tissue extracts and testing the histamine-choline hypothesis.

In rabbits under these conditions all tissue extracts produce a fall of blood pressure (Fig. 2), which is little, if at all, affected by atropine, while mixtures of histamine and choline produce either a small fall followed quickly by a rise or a pure rise before atropine, and always a rise after atropine (Fig. 3).

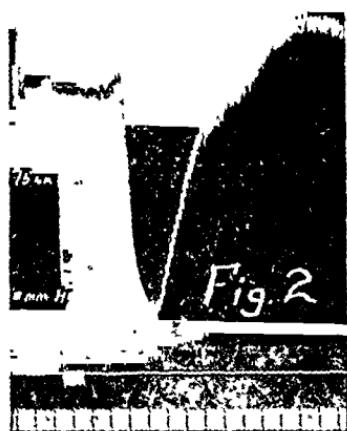


Fig. 2—Rabbit. Ether. 10cc solution of brain. (Before atropin.)

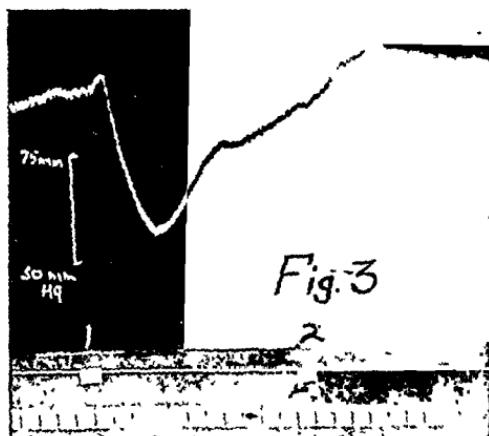


Fig. 3—Rabbit. Ether. (1) 10cc. saline extract of liver. (2) 10cc. histamine-choline solution. (0.1 mgm. aa.). (After atropin.)

The use of the rabbit eliminates the fall due to histamine, and atropine abolishes the depressor effect of choline; yet in the rabbit after atropine, in doses sufficient to abolish the action of the vagus as judged by direct stimulation, saline extracts of tissues produce a pronounced fall of blood pressure (Figs. 4a and 4b). Hence there would seem to be some substance contained in tissue extracts differing in its pharmaeo-dynamical and chemical properties from both histamine and choline (Figs. 5 and 6).

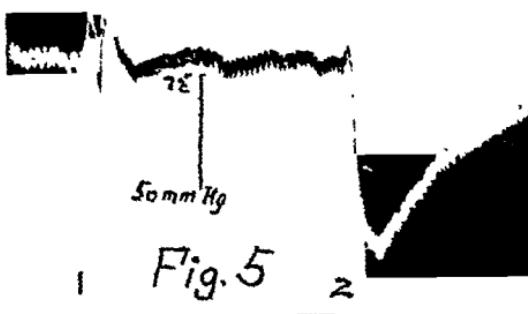
In the course of our experiments we had been constantly hindered by clotting in the cannula (though we were using the usually very efficient saturated sodium bicarbonate solution), especially during the injection of saline extracts. In one case at the end of an experiment we injected the usual dose of a fresh saline liver extract, more rapidly than usual, with the result that the rabbit died at once. On opening the heart im-



**DISCUSSION**

Fig. 4a—Rabbit. Ether. 10cc. saline extract of brain. (Before atropin.)

Fig. 4b—Rabbit. Ether. 10cc. saline extract of brain. (After 3cc. 1% atropin.)



**DISCUSSION**

Fig. 5—Rabbit. Ether. (1) 10cc. histamine-choline solution. (0.1 mgm. aa.)  
(2) 10cc. saline extract of brain.

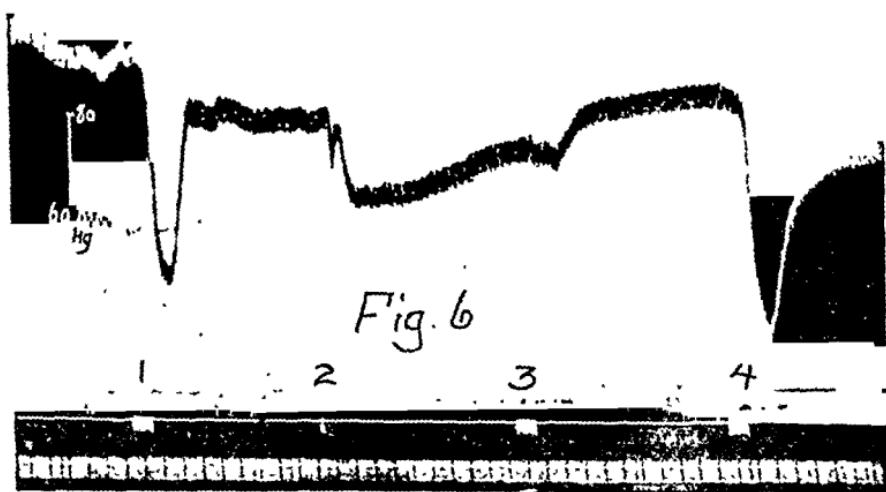


Fig. 6—Rabbit. Ether. (1) 10cc. saline extract of liver. (2) 3cc. 1% atropin.  
(3) 10cc. saline-ether extract of brain. (4) 10cc. saline extract of liver.

mediately, the right auricle and ventricle and pulmonary arteries were found full of thrombus.

Burke and Tait (9) in 1926 had meanwhile published the results of an investigation into the effect of tissue extracts on the coagulability of the blood, and as they showed that pulmonary thrombosis and embolism are of such frequent occurrence after the injection of tissue extracts, it seemed to us that here might be found the explanation for the fall of blood pressure produced in rabbits by tissue extracts, especially as rabbits were known to be unusually susceptible to intravascular clotting.

To eliminate the factors producing thrombosis we adopted the course advocated by Burke and Tait, viz., Pasteur-Chamberland filtration, which, as they showed, completely deprives an extract of its power to produce intravascular clotting.

Using this extract in rabbits and comparing its effect with that of the same extract treated in the ordinary way, we found that the fall of blood pressure is still obtained in both cases before or after atropine (Fig. 7).

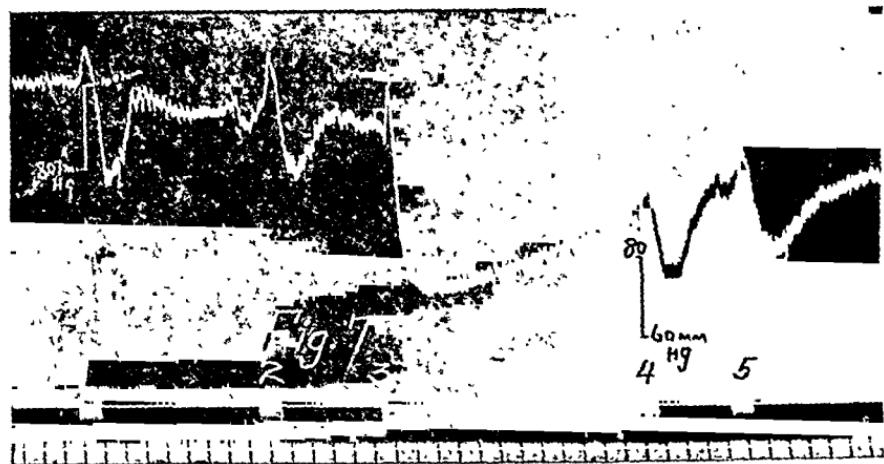


Fig. 7—Rabbit. Ether. (1) 10cc. Pasteur-Chamberland filtered saline extract of liver. (2) 10cc. saline extract of liver. (3) 4cc. 1% atropin. (4) 10cc. Pasteur-Chamberland filtered saline extract of liver. (5) 10cc. saline extract of liver.

A further procedure recommended to us in conversation by Dr. J. W. Pickering for ridding the extract of phosphatides was shaking with benzene. Here again using a tissue extract which was divided into two parts, one being shaken with benzene, little or no difference was observed in the effect of their injection on the blood pressure of the rabbit (Fig. 8).

It seems then that obstruction in the pulmonary circulation is not necessarily responsible for the fall of blood pressure produced by tissue extracts.

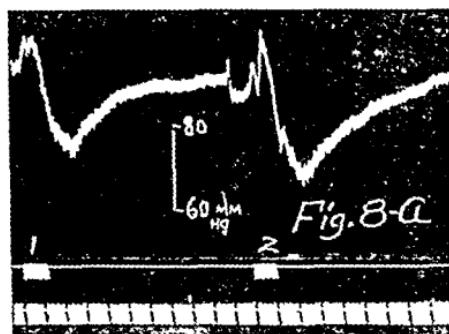


Fig. 8a—Rabbit. Ether. (1) 10cc. saline extract of muscle, shaken with benzene. (2) 10cc. saline extract of muscle. (Before atropin.)

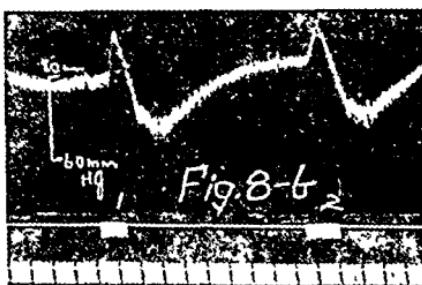


Fig. 8b—Rabbit. Ether. (1) 10cc. saline extract of muscle, shaken with benzene. (2) 10cc. saline extract of muscle. (After atropin.)

#### *Effects of Alcohol-Ether Extracts.*

As shown by Vincent and Sheen, a certain amount of depressor substance is soluble in ether after extraction with alcohol, though none is directly extracted by ether.

The active substance which goes into solution in ether consists apparently to a great extent of choline, as the depressor effect is nearly always abolished by atropine (Fig. 9a).



Fig. 9a—Cat. Ether. (1) 10cc. saline extract of liver (after Pasteur-Chamberland filtration). (2) 10cc. saline extract of liver.

A point of some significance is the level of the pressure at the time of injection. Using a cat with a blood pressure of

about 150 mm. Hg., a considerable fall of pressure is obtained on the injection of saline extracts of liver. If some hours later the animal is decerebrated so that its blood pressure is now about 40 or 50 mm. Hg., the injection of 10 c.c. of the same tissue extract produces merely such a rise as is produced by an equal quantity of saline. (See Fig. 9b.)



Fig. 9b—Cat. Decerebrated. Two successive injections 10cc. saline extract of liver.

In an animal whose blood pressure is low, saline usually produces a rise, though it fails to do so when the pressure is already high. These results have been obtained repeatedly.

#### SUMMARY

The depressor effect of tissue extracts cannot be accounted for on the assumption that their action is due solely to their histamine and choline content.

The fall of blood pressure produced in the rabbit is not due to temporary obstruction in the pulmonary circulation.

Tissue extracts do not produce a fall of blood pressure when the initial pressure is low (30-40 mm. Hg.).

The expenses of this research were defrayed in part by a grant to one of us from the Government Grant Committee of the Royal Society.

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# HYPERNEPHROMA IN A HORSESHOE KIDNEY

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Horseshoe kidney is not a rare anomaly. It was found once in every 142 operations on the kidneys at the Mayo Clinic<sup>1</sup>, while Carlier and Gérard<sup>2</sup>, in the extensive compilation of statistics from the literature of the world, collected 81 cases in approximately 69,000 autopsies, an incidence of one in 858. However, as far as we were able to ascertain, the case here presented is the first reported case of a hypernephroma occurring in such a kidney.

The case, aside from being unique, has several other unusual features, both from the clinical and pathological aspects.

## CASE REPORT<sup>3</sup>

E. J., white, aged 60, a widow, was admitted to the hospital December 2, 1925, complaining of polyphagia, occasional polydipsia, increasing weakness, pruritus vulvae, nocturia, chilliness, insomnia and pains in the first two toes of the right foot. A sister had diabetes. The patient had had three normal pregnancies and one miscarriage. Menopause occurred at 50. She had been under dietetic treatment for diabetes mellitus for several years and two years previously the distal portion of her right fifth toe had been amputated for gangrene. Five years ago she weighed 175 pounds, while at present her weight was 106½ pounds. Her physical examination disclosed evidence of emaciation, generalized arteriosclerosis, a firm globular enlargement of the thyroid and a dry gangrene of the distal portion of the right second toe. The urine was negative for sugar, acetone and diacetic acid and on microscopical examination showed an occasional hyaline cast. She had a slight anemia and her blood chemistry gave the following figures: Sugar 295 mg., CO<sub>2</sub> 71, Urea N. 16.6 mg., Creatinine 0.6 mg., Uric Acid 3.0 mg. Her temperature on admission was 99° F. and her basal metabolism +39%.

Commencing with a diet composed of protein 32 gms., fat 96 gms. and carbohydrate 30 gms., the amounts were gradually raised to protein 50 gms., fat 200 gms. and carbohydrate 70 gms., at which point sugar was found in the urine. In conjunction with increasing doses of insulin up to 15 units twice a day, her diet was then raised

\*From the service of Dr. DeWitt Stetten

to protein 100 gms., fat 200 gms. and carbohydrate 100 gms. without the appearance of sugar in the urine.

On January 11th, her blood sugar was 168 mg. and her CO<sub>2</sub> 63.3. On the 13th, the carbohydrate was increased to 130 gms. About this time, however, she began to do poorly. Her blood sugar was 250 mg. on the 28th and the gangrene, which had remained more or less stationary, slowly extended, so that by February 22nd it had involved the lateral surfaces of the foot and all the toes except the third. Sugar appeared in the urine February 14th and slowly mounted to 3.3% by February 23rd. Her temperature fluctuated between 99°F. and 101°F. On March 1st, the leg was amputated below the knee. She suddenly became worse on March 3rd and a blood chemistry on that day showed sugar 400 mg. and CO<sub>2</sub> 52.8. The urine contained 0.5% sugar and was positive for acetone and diacetic acid. In spite of large doses of insulin, hyperdermoclyses and colon irrigations with sodium bicarbonate, she lapsed into coma, and on the 5th her blood sugar was 660 mg. and her CO<sub>2</sub> 19.5. By the evening of the 6th, the blood sugar had been forced down to 74 mg. while her CO<sub>2</sub> had risen to 48.5. Pulmonary oedema developed and death followed.

#### AUTOPSY FINDINGS

The body was that of a well developed, elderly female, showing signs of marked emaciation. The eyeballs were rather prominent and there was a globular, cystic enlargement of the right lobe of the thyroid, the size of a small tangerine. The right leg below the knee was missing, the stump showing a clean, recent, unsutured, operative wound. Both upper lobes of the lungs showed senile emphysema, with oedema and a patchy pneumonia of the lower lobes. The heart weighed 450 grams, and showed hypertrophy of the musculature. The cusps of the mitral valve were somewhat shortened in width and their free edges were markedly thickened. The aorta contained many raised, firm, yellowish plaques scattered diffusely throughout its entire length. The gastric mucosa was congested. The intestines were apparently normal. The uterus and adnexae were atrophic. The spleen weighed 300 grams, and was densely adherent to the surrounding structures. It was rather soft and its cut surface was pale red in color and the pulp easily scraped off. The markings were not prominent. The liver was moderately enlarged, weighing 2100 grams. The capsule was smooth and glistening. On section, it had a mottled appearance, the centers of the enlarged acini being reddish brown and the periphery yellowish in color. The pancreas was somewhat reduced in size, its surface was irregularly nodular and its consistency markedly increased. The adrenals were enlarged, especially the left, which was about twice the normal size. The latter contained a yellowish nodule, about the size of a

grape, in its cortex. The kidneys were dystopic and joined together by their lower poles at the level of the promontory of the sacrum, in front of the great vessels. They converged slightly downward and inward and differed markedly in size. The left measured 16 cm. in length x 5.5 cm. in width x 3.5 cm. in thickness, while the right measured only 10 cm. in length x 5 cm. in width x 2.5 cm. in thickness. Their anterior surfaces showed the fetal lobulations, while the posterior surfaces were smooth. Situated in the bend of the horseshoe was a large circumscribed, globular tumor mass, 8 cm. x 3.5 cm. It was surrounded by kidney tissue laterally and above. The pelvis were single, discrete and rotated anteriorly. The right

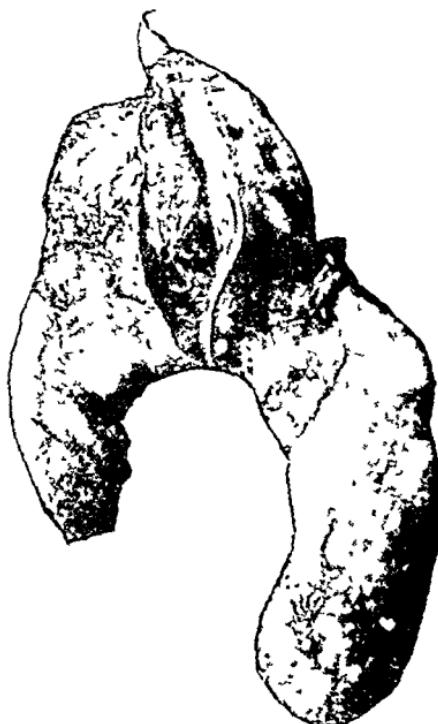


Fig 1 Hypernephroma in Bend of Horseshoe Kidney (Posterior View)

pelvis was enlarged, flattened out and markedly irregular in shape. The right ureter coursed over and was adherent to the anterior surface of the tumor. On section, the tumor presented a large central area composed of glistening, firm, grayish white tissue, containing many small butter-yellow islands. Around the periphery were several similar, though larger islands, some of which exhibited areas of softening and hemorrhage. (See Fig. 1.)

#### MICROSCOPICAL EXAMINATION

The lungs showed marked tortuosity and congestion of blood vessels, oedema and small areas of bronchopneumonia in the lower

lobes. The heart showed a hyaline degeneration of the muscle fibres and a slight interstitial fibrosis. The spleen was congested and showed an increase in the pulp cells and a slight fibrosis of the reticulum and trabeculae. There was a diffuse parenchymatous degeneration and slight fatty infiltration of the liver cells. There was a marked overgrowth of the interstitial fibrous tissue and atrophy of the parenchyma of the pancreas. The number of islands of Langerhans was diminished and scattered throughout the acinous tissue were small fibrous nodules, probably replaced islands. The adrenal cortex contained a very vascular adenoma, composed of typical adrenal cells, rich in lipoid. A small septic infarct was also present in the cortex. It was irregular in shape and consisted of a central area of cortical tissue in all stages of necrosis and disintegration and a peripheral zone of pus cells. A few lymphocytes and mononuclear cells were seen. (Figs 2. and 3.)



Fig. 2—X 250 Adenoma of Left Adrenal.



Fig. 3—X 250 Septic Infarct of Left Adrenal.

Sections through the tumor revealed collections of large, foamy, partly transparent, polygonal, plant-like cells, arranged either in small circular groups or as cords or sheets of cells separated and supported by a small amount of fine, extremely vascular connective tissue. In one area, the cells enclosed lumina-like spaces and had a papillary structure. The tumor cells showed marked hydropic degeneration and extensive necrosis. Small hemorrhages were frequent and in the necrotic area were several cystic spaces filled with blood. A large venous thrombus was seen containing an unusual number

of polymorphonuclear leucocytes. There was a slight round celled infiltration in a few localized areas.

*Anatomical Diagnosis:* Cystic goiter; Senile emphysema; Bronchopneumonia; Myocardial degeneration; Chronic endocarditis of mitral valve; Hypertrophy of both ventricles and dilatation of the right; Athero-sclerosis; Acute splenic tumor; Parenchymatous degeneration liver; Chronic interstitial pancreatitis; Adenoma and septic infarct of adrenal; Hypernephroma in horseshoe kidney; Amputated right leg.

#### COMMENT

As far as we were able to discover, only two cases of tumor in a horseshoe kidney are reported in the literature. Both, however, were sarcomas, limited to the right kidney, and affected very young children. The first, mentioned by Hildebrand<sup>3</sup> in 1894, was more fully reported by König and Pels-Leusden<sup>4</sup> in 1900, and the second was published by Gibbon<sup>5</sup> in 1909.

Besides the unusual type of tumor present in our case of horseshoe kidney, its situation in the bend of the horseshoe is also of interest.

Since Blum<sup>6</sup> in 1901 discovered that the subcutaneous injection of adrenal extract produced glycosuria, numerous workers have studied the relationship of epinephrin to carbohydrate metabolism. Metzger<sup>7</sup> proved that the glycosuria was due to an increase in sugar in the blood, and Vosburgh and Richards<sup>8</sup> and Iwaroff<sup>9</sup> showed that the overproduction of glucose depended upon an accelerated breaking down of glycogen in the body. Macleod and Pearce<sup>10</sup> found that the injection of epinephrin into portal circulation of living animals was followed by an increased glycogenolysis in the liver, while Ringer<sup>11</sup> after making animals glycogen-free by a combination of hunger, cold and phloridzin, found no change in the elimination of sugar or in the D:N ratio. Cannon and his co-workers<sup>12</sup>, using the denervated heart as an indicator, have clearly demonstrated the antagonism between the glycogenolytic action of the medulli-adrenal secretion and the glycogenetic action of insulin in the maintenance of the glycemic equilibrium.

In our case, the presence of a septic infarct in the adrenal with consequent irritation and over-secretion of epinephrin may well explain the sudden increase in the severity of the diabetes in spite of a restricted diet and fairly large doses of insulin.

The day before the patient's death, although practically on a starvation diet, her blood sugar rose to 660 mg. The source of this high blood sugar level is easily understandable on the basis of an increased glycogenolysis incident to an hyperadrenalinemia.

The origin of the infarct was, in all probability, the thrombosed vessels in the gangrenous toes. In fact, the turning point in the progress of her illness was coincident with a pronounced extension of the gangrene to the foot.

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## HYPOTHYROIDISM AS A COMPLICATION OF DIABETES MELLITUS

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Hypothyroidism as a complication of juvenile diabetes deserves special comment. Marked hypothyroidism was recognized three years ago in a diabetic girl of fifteen years, on her return to my office for routine supervision two months after she had left the sanitarium. Her metabolic rate at that time was minus 38%. Her record during the first month of insulin therapy was reported (1) because of a severe lipemia and lipemic retinalis. No discussion of her hypothyroidism, however, was given. During these three years, it has been necessary to continue thyroid therapy which has been controlled by metabolic rate determinations.

During the last three years, hypothyroidism has also been observed in several other diabetic children and young adults. Thus the realization of such a possible complication, especially in the young diabetics, seems important to keep in mind. The presence of physical and mental sluggishness, dry skin and hair, slow pulse, and in some cases a gain in weight, should suggest the possibility of hypothyroidism.

A study of a series of young diabetics from the point of view of possible hypothyroidism is in progress. This report includes metabolic rate determinations and a discussion of the symptomatology and treatment of the patients with hypothyroidism.

It is realized that the metabolic rate is diminished with under-nutrition. Our cases, however, are all receiving sufficient calories, and the diabetic condition in each patient is controlled satisfactorily with insulin.

This preliminary report is given at this time because of the absence in the literature of any emphasis on hypothyroidism as a complication in the young diabetic.

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## Book Review

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DIE KASTRATION BEI WIRBELTIEREN UND DIE FRAGE VON DEN SEXUALHORMONEN. Knud Sand, in Handbuch der Normalen und Pathologischen Physiologie, Berlin, 1926. Julius Springer.

This section of the Handbuch comprises the following articles by Dr. Sand:

1. Die Kastration bei Wirbeltieren und die Frage von den Sexualhormonen.
2. Transplantation der Keimdrüsen bei Wirbeltieren.
3. Der Hermaphroditismus bei Wirbeltieren in experimenteller Beleuchtung.
4. Die Keimdrüsen und das experimentelle Restitutionsproblem bei Wirbeltieren.

Sand presents an excellent, well illustrated summary of the evidence on each of the topics treated.

# Abstract Department

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**Microspirometric researches on hormones (Mikrorespirometrische Untersuchungen über die Hormonwirkungen).** I. Insulin. Ahlgren (G.), Skandin. Arch. f. Physiol. (Leipz.), 1926, 47, 271-280.

Using a microspirometer, Ahlgren found in eight experiments that O<sub>2</sub> consumption and CO<sub>2</sub> production by minced frog muscle was augmented by adrenalin in concentrations of 1:10,000,000 to 1:100,000,000,000. More concentrated solutions depressed the gas metabolism.—R. G. H.

**The effects of epinephrin on the response of the frog heart to stimulation of the accelerator nerve.** Barlow (O. W.) & Sollmann (T.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, 28, 157-158.

During acceleration produced by perfusion of the frog heart with solutions, diminution of response from stimulation of the accelerator nerve was closely proportional to the degree of epinephrin augmentation, even after depression of the cardiac musculature has reduced the amplitude. Augmentation by the heart perfused with Ringer solution occurs in about the same degree from both epinephrin and from stimulation of the accelerator.—C. I. R.

**The role of the suprarenal gland in the natural resistance of the rat to diphtheria toxin.** Belding (D. L.) & Wyman (L. C.), Am. J. Physiol. (Balt.), 1926, 78, 50-55.

It is known that double suprarenalectomy increases the sensitivity of rats to a variety of poisonous drugs and toxins, and that rats have a high natural resistance to diphtheria toxin. Both suprarenal glands were removed from albino rats in one operation and the control rats received the same operative procedure except the removal of the glands. The highest post-operative mortality in the suprarenalectomized animals occurred with fluctuations in room temperature and rectal measurements indicated a lessened ability of the suprarenalectomized rats as compared with the controls to maintain their body temperature in a cold atmosphere. An approximation of the lethal dose of diphtheria toxin administered intraperitoneally two to three weeks after operation showed that the controls were about two and one-half times as resistant to the toxin as the suprarenalectomized rats. The amount of diphtheria toxin in the blood four hours after an intraperitoneal injection of one M.L.D. per gram of body weight was measured by the Roemer

intradermal method in guinea pigs. The suprarenalectomized rats had approximately 2.75 times as much free toxin in their blood as the control rats. Suprarenal deficiency apparently renders less effective the normal mechanism of the rat for the elimination or destruction of diphtheria toxin.—D. L. Belding.

**Spurious hermaphrodisim of suprarenal origin (Zur Kentniss der suprarenalen Pseudarrhenic).** Feldmann (E.), Arch. f. path. Anat. u. Physiol. (Berl.), 1926, 259, 608-616.

The case of a child, 7 years old, with well proportioned male external genitalia and only female internal sex glands is described. There was an accompanying enlargement of the adrenal glands involving only the cortex. In fact, the medulla seemed hypoplastic. The author holds that this hyperplasia of the adrenal cortex was probably present from very early embryonic life and was the causative factor in the production of the disturbed development of the sexual organs.—W. J. A.

**Carcinoma of cortex of suprarenal gland with virilism.** Feinblatt (H. M.), Arch. Int. Med. (Chicago), 1926, 38, 469-473.

A young woman progressively developed virile characteristics, including facial hypertrichosis, the masculine type of abdominal and axillary hair, a low pitched voice and a masculinoir facies. Later, a tumor was palpated in the region of the right kidney. Necropsy revealed a large carcinoma of the cortex of the right suprarenal gland with extension by way of the vena cava, but without distant metastasis.—Author's Summary.

**The maximum metabolism and the suprarenal capsules.** Giaja (J.) & Chabovitch (X.), Compt. rend. Acad. d. sc. (Par.), 1925, 181, 885-886.

The authors have shown in three rat experiments certain modifications in thermogenesis resulting from the removal of the adrenals: 1, decapsulated rats are unable to accommodate their thermogenesis; 2, maximum metabolism is lowered to a point confusing it with basal metabolism; 3, injection of .4 mgs. of adrenalin increases the respiratory quotient; the normal maximum of metabolism, however, is never reached. From these facts they conclude that the adrenal capsules play an important role in thermogenesis.

—C. M. MacFall.

**The effect of nephrectomy and suprarenalectomy in the rat on resistance.** Gottesman (Jessie M.) & Gottesman (J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 24, 45-48.

The authors summarize as follows: "It has been shown that the duration of life of nephrectomized rats is not affected by injec-

tions of the same typhoid vaccine which regularly shortens the life of suprarenalectomized rats. It has also been shown that suprarenalectomized rats have a refractory period of approximately four days before any marked drop in resistance is manifest. These findings, together with the fact that the suprarenalectomized animals fully retain their ability to form anti-bodies and to regenerate the thymus and lymph tissues, suggest that suprarenalectomy exerts a specific physiologic influence on resistance."—J. C. D.

**The influence of burns on epinephrin secretion.** Hartman (F. A.), Rose (W. J.) & Smith (E. P.), Am. J. Physiol. (Balt.), 1926, 78, 47-49.

Experiments on anesthetized cats show that burns cause an increase in the epinephrin output (dilatation of completely denervated iris). The increased output sometimes persists for a few hours. There was depletion of epinephrin and of lipoids in the adrenals of these animals. Therefore, burns cause an excessive activity of the adrenals.—Author's Summary.

**The effects of bilateral suprarenalectomy on the life of rats.** Jaffe (H. L.), Am. J. Physiol. (Balt.), 1926, 78, 453-461.

Ninety rats were followed for a period of 1 year after suprarenalectomy and upon analysis were divided into 3 groups. The first group, 35%, died within 30 days after operation from acute and subacute insufficiency, a great majority of deaths occurring before the 13th day. The second group, comprising 46% of the total, consisted of animals which survived suprarenalectomy for many months, but which were chronically insufficient and suffered from progressive emaciation resulting in marked or complete absence of fat, asthenia, and lowered resistance leading in some instances to snuffles and skin infections. Most of these animals died within 7 months after operation, no gross accessories being found at autopsy. The syndrome of chronic suprarenal insufficiency in rats has never been adequately emphasized. The third group, 19% of the entire series, consists of animals in which suprarenalectomy is followed by no demonstrable clinical effects. These animals are biologically normal rats in every respect, and large accessory cortical masses are always found at autopsy. When rats are studied clinically for many months after suprarenalectomy, the seriousness of this operation in regard to the ultimate life of the animal becomes evident. Contrary to the reports in the literature, we found that fully 80% of rats die from the effects of suprarenal removal within a year after operation.—Author's Abstract.

Central stimulation of the adrenals and the paraganglia during insulin intoxication (Ueber die zentrale Reizung der Nebennieren und der Paraganglien während der Insulinvergiftung). Kahn (R. H.), Arch. f. d. ges. Physiol. (Berl.), 1926, 212, 54-63.

The results of H. Poll, indicating that after insulin intoxication in the mouse morphological changes are found in both portions of the adrenals, are confirmed for the rabbit and for the dog. In the dog the changes are also apparent in the abdominal chromaphil body. The chromaphil tissue so changed shows a diminution of its adrenaline content. In rabbits the toxic action of insulin on the adrenal medulla takes place through nerve channels, since sectioning of the splanchnic protects the adrenal from these changes. Hence it would appear that insulin acts through the central nervous system on the paraganglia, comparably to the actions following sugar-puncture, asphyxia, etc. The morphological changes recorded are diminution of the size of cells, formation of vacuoles, lessening of the color-staining reactions, and disappearance of granules.

—A. T. C.

Rôle of suprarenals in blood sulphur regulation. Loeper et al., Presse méd. (Par.), 1926, 34, 1209-1211; Abst. J. Am. M. Ass., 87, 1689-1690.

The authors noted an increase of blood sulphur in three cases of Addison's disease; the proportion of the oxidized sulphur was reduced, while that of the neutral sulphur was increased. Analogous phenomena were observed in dogs after removal of a suprarenal. Further experiments showed that the blood of the suprarenal artery contains much more sulphur than that of the corresponding vein and that in the artery the proportion of oxidized to neutral sulphur is lower than in the vein. It appears evident that the suprarenal glands retain a part of the blood sulphur, especially of the neutral. This was confirmed on large numbers of the suprarenal glands of sheep. A part of this sulphur is utilized for formation of the suprarenal pigment. Melanoderma, they hold, is the consequence of an exaggerated elimination by the skin of the sulphur retained in excess in the blood, in conditions in which suprarenal function is impaired.

Antagonism of barium chloride and glandular extracts on chromatophores by epinephrin and ephedrine. Nadler (J. E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 24, 53-54.

In the squid epinephrin antagonizes extracts of the parathyroid and of the anterior and posterior lobes of the hypophysis more intensely than ephedrine. The latter is more effective in antagonizing barium chloride.—J. C. D.

**The effect of epinephrin and prolonged accelerator stimulation on the response of the frog heart to stimulation of the cardiac-inhibitor nerve.** Sollmann (T.) & Barlow (O. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, 28, 159-164.

Response of the frog heart to stimulation of the vagus is increased by perfusion with epinephrin and by continuous stimulation of the accelerator nerves, and the inhibitory response becomes progressively greater the longer the perfusion or accelerator stimulation are continued and recovery after discontinuance of these procedures is quite slow. The authors suggest that these results are due to accumulation of muscular metabolites.—C. I. R.

**The effects of fatigue and temperature on the adrenal bodies of the rat.** Vincent (S.), Quart. J. Exper. Physiol. (Lond.), 1925, 15, 319-326.

White rats, exercised at a room temperature of about 14.5°C., exhibit a fall of body temperature and a marked reduction of the chromaphil reaction of the adrenal medulla. Exercise at 18-20°C. results in no change in body temperature, but above 20°C. there is an increase in body temperature. Under these conditions there is no change in the chromaphil reaction. The author concludes that any effect of exercise upon the chromaphil reaction is secondary to the lowering of body temperature.—P. M. Harmon.

**The influence of organ extracts and especially of extract of corpus luteum on the blood-coagulation time (Der Einfluss von Organextrakten im besonderen von Corpus-luteum-Extrakten auf die Blutgerinnungszeit).** Alzinger (F.), Arch. f. d. ges. Physiol. (Berl.), 1926, 213, 548-555.

Organ extracts were made by boiling 20 minutes with water or with alcohol or ether, cooling and filtering. Sodium chloride was added to the first to 0.85%, while the latter was evaporated to dryness and the residue dissolved in 0.85% sodium chloride solution. Such extracts of corpus luteum, liver, spleen, or ovary produced definite effects on the coagulation time, aqueous extracts slowing and alcoholic and ether extracts hastening it. The accelerating compounds are soluble in alcohol and ether and thermostable. The difference of effect is more marked the lower the temperature.

—A. T. C.

**The heart regulating hormone of the liver and other pharmacological effects of the same (Das Herzregulierende Hormon der Leber und die Aenderung Pharmakologischer Wirkungen Durch Das-selbe).** Asher (L.), Schweiz. Med. Wchnschr. (Berl.), 1926, 56, 921.

Asher states that he has been able to isolate a hormone from

the liver which increases the strength of the heart beat, increases the heart rate, and diminishes the vagus irritability. This substance may be described as an agent which assists sympathetic action. Liver extracts were prepared from liver powder. The exact nature of the process is not stated. The liver extract produced a slowing of the pulse and elevation of blood pressure. Tests for the presence of bile salts were negative. The liver hormone which has been obtained by perfusion of liver has a different action from that of liver extract. Experiments with sodium cholate show an action similar to that of the liver hormone, and Asher believes that they are probably identical. Asher emphasizes that the cholate is nitrogen free, and is therefore a hormone which does not belong to the group of amines to which so many other hormones belong.

—R. H. Major.

**Further observations on patients with hypertension and increased basal metabolic rate.** Boas (E. P.) & Shapiro (S), American Heart Journal (St. Louis), 1926, 1, 643.

A group of patients is described in which are presented the following clinical characteristics: hypertension (systolic and diastolic), increased basal metabolic rate, tachycardia, nervousness, loss in weight, and pigmentation of the skin. It is believed that these symptoms constitute a special syndrome which should be distinguished from both exophthalmic goiter and uncomplicated hypertension. Including those mentioned in a previous communication, ten such cases are described by the authors.—Author's Abst.

**Endocrine glands in allergy.** Duke (W. W.), in Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy. The C. V. Mosby Co. (St. Louis), 1925, 145-146.

The organs of internal secretion evidently play a marked role in the symptomatology of reactions of hypersensitiveness (allergy). This should seem self-evident when we bear in mind that the great majority of cases, regardless of their severity, can be completely relieved through the action of adrenalin. Many cases relieved by pituitary extract. If adrenalin has a normal physiologic antagonist, and one might easily believe that this is the case, an overproduction in this might, on theoretical grounds, give rise to a reaction. Thyroid extract in occasional cases is beneficial especially in patients whose metabolism is below par and whose temperature runs markedly subnormal. The above influences from a practical viewpoint are effective in many cases, but would seem usually to be secondary factors in the etiology of reaction.—R. G. H.

**Endocrine glands of rabbits fed cod liver oil or irradiated cholesterol.** Gates (F. L.) & Grant (J. H. B.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 24, 59-62.

Neither treatment appreciably influenced the weights of the ductless glands.—J. C. D.

A study of jaw and arch development considered with the normal and abnormal skeleton. Howard (C. C.), *The International Journal of Orthodontia, Oral Surgery and Radiography* (St. Louis), 1926, 12, 3-16.

Howard's studies indicate that conditions met by the orthodontist are frequently associated with other anomalies that render evident their endocrine etiology. Adequate treatment often necessitates consideration of this etiology, local measures being of merely temporary benefit. On an examination of over six hundred cases in the Good Samaritan Endocrine Clinic, forty-one obese subjects of posterior lobe pituitary deficiency were found. All had normal arch and jaw development, with almost perfect teeth. Nineteen cases of hypothyroidism or Mongolian idiocy were seen. All showed congenital absence of teeth—from one to twelve each.—R. G. H.

**Studies on the conditions of activity in endocrine glands. XVIII.**

**Locus of the calorigenic action of adrenalin with observations on tissue metabolism.** Hunt (H. B.) & Bright (Elizabeth M.), *Am. J. Physiol.* (Balt.), 1926, 77, 353-369.

Amytal anesthesia increases the resting metabolism of the cat about 10%. The basal rate of metabolism in muscle is low, 0.50 to 1.0 calorie per kilo per hour. In the liver it is high, 10 to 20 calories per kilo per hour. In the other viscera it averages 2 to 3 calories per kilo per hour. Adrenalin given in a dosage of 0.005 mgm. per kilo per minute for six minutes, produces rises in total metabolism which averages 10.6% during the following 20-minute period. The peaks of the rises average 19.0%. The increased metabolism of the heart would account for only one-third of this total rise. Adrenalin has a general calorigenic action on tissue metabolism.—Author's Summary.

**The basal metabolic rate in cases of chronic cardiac disease and in cases of hypertension.** Shapiro (S.), *Arch. Int. Med.* (Chicago), 1926, 38, 385.

The metabolic rates determined under strictly basal conditions were studied in a series of forty-two cases of heart disease, including twenty-two patients with valvular lesions, fifteen with hypertension and cardiac hypertrophy, two with congenital heart disease and three with functional tachycardias. In three cases the basal metabolic rate was found to be definitely elevated above normal. These three patients had dyspnea or hyperpnea. In the remaining thirty-nine cases of heart disease unaccompanied by dyspnea at rest the basal metabolic rates were within the accepted normal limits. The

author concludes, therefore, that the basal metabolic rate in patients with organic heart disease is normal. High readings are usually due to dyspnea. The cardiac overactivity which occurs in a heart compensating for an organic heart defect or maintaining an elevated vascular tension does not detectably elevate the heat production.—Author's Abst.

**The calcium content of the blood.** Waldorp (C. P.), *Prensa médica argentina* (Buenos Aires), 1926, **13**, 140; Abst. *J. Am. Ass.*, 1926, **87**, 1163.

Waldorp's extensive study of the calcium content of the blood confirms the influence of the nervous system on the fluctuations. The subject should be kept quiet before testing the blood calcium with intravenous injection of a given quantity of calcium. The resulting hypercalcemia lasts in normal conditions for an hour and then the calcium returns to the former level. In 26 cases of thyroid disease with high basal metabolism, the blood calcium content was low; in 9 of 18 cases the sugar content was abnormally high. The calcium content kept persistently low in a case of hypothyroidism and in 3 cases of exophthalmic goiter under thyroid treatment. The calcium content was below normal also in 4 cases of acromegaly and in one of a pituitary tumor. The calcemia in the latter case fluctuated with the increased or decreased functioning of the anterior lobe of the pituitary. In 3 cases of eunuchoidism the basal metabolism was high in 1, with low calcemia, but in the 2 others both were within normal range. His research on the parathyroids confirms their fundamental roles in the maintenance of normal calcemia.

**The relation between corpus luteum and the mammary gland.** Drummond-Robinson (G.) & Asdell (S. A.), *J. Physiol. (Lond.)*, 1926, **61**, 608-614.

The investigation failed to throw any light on the question whether mammary development may occur in the absence of the corpus luteum if the foetus is present, since abortion always followed the removal of the corpus luteum. Clean-cut evidence, however, was obtained as to the relation between corpus luteum and mammary growth and function. In this work virgin goats were used, care being taken to select animals which had not been bred for high milk production. The sire was the same in all cases. The removal of the corpus luteum was timed with reference to the appearance of abundant globulin secretion and the beginning of mammary proliferation, which events occur both in goats and in cows at about the middle of gestation. Some of the operations were performed well before this time and some after it. When performed before the globulin stage of the gland was reached milk was not

secreted. Removal of the corpus luteum after the globulin stage was reached was followed by an immediate copious secretion of milk. After the stimulus for growth has been given by the corpus luteum the mammary cells seem able to attain the globulin stage without further continued stimulation, but if the stimulus is removed by excision of corpora lutea the attainment of the globulin stage is not followed by milk secretion. The postulation of an inhibitory hormone to account for the usual decline of milk secretion in late pregnancy is unnecessary since it seems unlikely that cells stimulated to growth and division by the corpus luteum at the half-way stage of pregnancy can continue to secrete.

—E. P. Durrant.

**A study of the effects of testicular extract upon the pregnant guinea-pig and the fetus.** Emery (F. E.), Tr. Am. Micr. Soc. (Buffalo), 45, 44-53.

Virgin female guinea-pigs and females that were kept with males were injected intraperitoneally for a period of six months with saline extracts made from desiccated testicular substances. The general systemic reactions in the injected animals were evidence of pain at the area where the injections were made, watering of the eyes and occasionally coma, but rarely death. Chronic peritonitis developed in most of the animals. Histological examinations of the ovaries of the injected animals showed marked degenerative changes with atrophy of the Graafian follicles and a tendency to cystic formation. This condition was more marked the younger the animal at the beginning of injection. The young born from injected mothers were apparently normal with regard to weight, the ratio between males and females, and fertility. Histological examinations of the gonads of the young born from treated mothers showed the testes were normal, but the ovaries were shrunken and there seemed to be more atresia of the Graafian follicles than in normal animals. The power of reproduction in the females that were injected seemed to be more closely correlated with the degeneration produced in the ovaries than with the general emaciation, because the animals, in many instances, did not breed for considerable periods after they had apparently recovered their normal weight. In control animals injected with ovarian extract and amniotic fluid degenerative changes in the ovary were not so marked and cystic formation was rare.—Author's Summary.

**Female sex hormone.** Frank (R. T.) & Goldberger (M. A.), J. Am. M. Ass. (Chicago), 1926, 86, 1686-1687; Abst. A. M. A.

Frank and Goldberger have obtained the female sex hormone from blood specimens by means of lipoid extraction performed under

identical conditions by identical methods. The results are sufficiently concordant to be considered quantitative. Blood has been obtained from 38 patients. In some instances, specimens have been taken at intervals of from 5 to 7 days through two monthly cycles from the same patient. From this investigation it has become evident that:

1. The amount of female sex hormone found in the circulating blood of the human female varies during the menstrual cycle. An abrupt increase takes place beginning between the tenth to the fifteenth day counted from the first day of the last menstruation.
2. The female sex hormone is present in greatest concentration in the circulating blood near the first day of menstruation.
3. With the onset of menstruation, the female sex hormone abruptly diminishes in the general circulation.
4. The female sex hormone appears in the menstrual blood, there being present in from triple to six fold the concentration found in the circulating blood.
5. In certain types of menorrhagia and metrorrhagia, the female sex hormone may be (a) absent from both the circulating and the uterine blood; (b) in others, present in both the circulating and the uterine blood.
6. In certain amenorrheas, an increase in amount of the female sex hormone may be demonstrated in the circulating blood.

From these observations, the authors feel justified in concluding that:

- (a) The female sex hormone secreted by the maturing follicle reaches the general circulation.
- (b) The sudden increase of female sex hormone found from 10 to 15 days after the last menstruation may be used approximately to determine the time of ovulation.
- (c) The female sex hormone secreted by the corpus luteum likewise reaches the general circulation, continuing the pregravid stimulation of the genital tract and breasts as demonstrated by other methods in a previous communication.
- (d) During the pregravid stage, either (1) a concentration and storage of the female sex hormone takes place in the uterine tissues, or (2) the uterine mucosa at the time of the menses filters out the female sex hormone from the circulating blood.
- (e) Two types of menorrhagia or metrorrhagia occur, the one with oversecretion, the other with undersecretion of the female sex hormone. Further study may enable us to elaborate proper forms of treatment based on the etiology.
- (f) Some amenorrheas may be due to persistence of the corpus luteum, as evidenced by a persistence and undue concentration of the female sex hormone in the circulating blood.

**X-ray treatment of hypofunction of the ovary, with special reference to the regulation of menstrual function.** Hirsch (I. S.), Radiology, 1926, 7, 93.

The method of treatment has been called the stimulative treatment of the ovary. In certain cases, menstruation—irregular in interval, duration and amount, occasionally scanty and occasionally

profuse—cannot be ascribed either hypo or hyper, but to a dys or a disordered function, in which X-ray treatment acts as a regulator. The form of ovarian hypofunction suitable for this therapy may manifest itself as an amenorrhea, oligo-, opso- or a combined form and as an associated sterility. In all the types of cases suitable for treatment, there must be direct or indirect evidence that ovarian tissue exists in sufficient amounts to respond to the action of radiation. The numerous forms of treatment for the menstrual disturbance resulting from the insufficiency of ovarian function have all of them been of so little permanent value that there is justification in stating that there is no medicinal therapy which is definitely able to influence ovarian function. This applies to medication, physical measures, hydro or thermotherapy, active and passive gymnastics, massage, etc. The connection of the endocrine glands with the function of the genital apparatus has been recognized in recent years as quite definite for the ovaries, the thyroid, the pituitary, and the adrenal glands. Consequently, the administration of glandular extracts, either single or in combination (for instance, of entire ovary or liquor folliculi, corpus luteum, thyroid, the anterior and posterior lobes of the pituitary gland), has become quite customary in gynecological therapeutics. The results have been, however, neither striking nor permanent. The X-ray treatment consists in the administration of a small dose of radiation to each ovary. The dose necessary to produce the desired effect is 15 per cent of the castration dose delivered to each ovary through four portals. It is necessary to treat both sides because of the alternate ovulation. The four portals which take in all the pelvic structure may be irradiated at one sitting, or a portal at a time with intervals of a day or two. The series should not be repeated until after a lapse of several months. A slight variation from the 15 per cent may be necessary, depending (1) on the age, (2) thickness of abdominal wall, (3) duration of ovarian hypofunction. There should be no irradiation sickness, and no change in the skin of the portals treated. This treatment is contra-indicated in symptomatic amenorrhea, associated with such general systemic diseases as lues, tuberculosis, nephritis, pernicious anemia, also when secondary to adnexal disease, tumors or cystic disease of the ovary. Amenorrhea in advanced age or of very long duration, or that resulting from curettages after numerous abortions, does not respond to this treatment. In dystrophy-adiposo-genitalis, the involvement of other endocrines may necessitate other treatment. Thirty-six cases were studied. The result showed that in twenty-two of the cases treated, menstruation appeared after the treatment and in the majority of cases followed during the entire period of observation, and that the somatic and physical symptoms of the ovarian hypofunction disappeared rapidly after menstruation set in.

The longest period of amenorrhea to be followed by a menstruation after the irradiation was six years. Successful results were obtained in a woman of 30 years who had not menstruated for three years, in a woman of 28 who had not menstruated for two years, and in a woman of 34 years who had not menstruated for seventeen months. The interval between the first radiation and the menstruation varied, but in the majority of cases it was about twenty-eight days. In two cases the duration was two and three weeks, respectively. In some of these cases, simultaneously with the regulation of menstruation, dysmenorrheal symptoms were favorably influenced. In other cases there was no improvement of menstrual function. In some cases the pain with the first menstruation was very severe. In some cases of oligomenorrhea the increase of the menstrual function was abnormal. In certain cases of hypomenorrhea, in which there was a marked adiposity with the menstrual disturbance, the adiposity was reduced after the onset of menstruation, without any other therapeutic measure. One of these cases lost thirteen pounds after the treatment, one lost forty-seven pounds and one sixty pounds.

Besides this, there are seven cases treated for hypomenorrhea in which, following regular menstrual periods, pregnancy ensued. Out of five births there were four healthy children. The action of the radiation is to produce degeneration and retrogression of the graffian follicle whose secretory activity exercises an inhibitory effect in preventing further follicular rupture, ovulation and therefore menstruation. The results of this form of treatment lead to the conclusion that a certain dosage of radiation in carefully selected cases is capable of producing improvement in ovarian function, as shown by the regulation of menstruation and the induction of pregnancy, with the birth of healthy children. There cannot be any objection to this form of treatment on the ground that the already diminished ovarian activity can be still further diminished by the small doses of radiation. If the condition of the ovary is such that this should actually take place, nothing is lost, for such an ovary is hopelessly incompetent to produce the menstrual mechanism, or to produce an ovum capable of fecundation.

—Author's Abstract.

The effect of different ovarian constituents on the blood sugar content (Zur Frage der inneren Sekretion der Sexualdrüsen. VII. Mitteilung. Ueber die Einwirkung der verschiedenen Ovarialbestandteile auf den Blutzuckergehalt). Kylin (E.), Ztschr. f. d. ges. Exper. Med. (Berl.), 1926, 51, 599-602.

Using chiefly ovaries of the cow, the author injected subcutaneously into dogs a watery extract of graafian follicles, corpora lutea and ovarian parenchyma. With the follicular extract a rise in blood sugar followed in all cases. With extract of corpus

luteum a fall in blood sugar resulted. No uniform results were obtained from parenchyma extract. This latter was not unexpected, since the ovarian residuum doubtless contained remnants of old corpora lutea and a number of small follicles which had not been removed. As Collip has shown, an insulin-like substance can be obtained from the most diverse organs of the body, and though its presence might be explained as a local storage from the Islands, yet it must be considered as possible that the corpus luteum might produce a substance with insulin-like effects. In the course of the researches described extracts made from the ovaries of a 28-year-old mare gave results exactly opposite those from cows of sexually functional age. As this age seems to be at least equal to the climacteric in the human species, experiments are planned to determine whether there is in the ovary an inner secretion peculiar to the post-climacteric ovary, with a view to possible light on the various pathologic manifestations associated with that epoch.

—E. P. Durrant.

**Ovarian hormone and metabolism.** Lacquer, E. et al., Deutsche med. Wchnschr. (Berl.), 1926, 52, 1331; Abst. J. Am. M. Ass., 1926, 87, 1425.

Lacquer, Hart and de Jongh observed an increased metabolism in castrated female rats after injections of ovarian hormone. The hormone is quite stable. The crude preparation in oil resists heating to 360° C.; the pure aqueous solution resists 170° C. It may be boiled in 26% potassium hydroxide or in 26% sulphuric acid. It is easily adsorbed—even by a filter paper. It resists pepsin and trypsin, but hardly acts by mouth—perhaps because of adsorption.

**Studies on the oestrous cycle in the rat. III. The effect of low environmental temperatures.** Lee (M. O.), Am. J. Physiol. (Balt.), 1926, 78, 246-253.

A study of the length and character of the oestral cycle was made in two groups of albino rats, one series (16) of which was kept under rather constant conditions of room temperature (22° C.), while the other (15) was kept out of doors during the three coldest months of the winter of 1924-25 (December, January and February). The series under room temperatures showed normal oestrous cycles of 4.8 days average length throughout the period. The experimental animals showed cycles of the same average length as the controls during a preliminary period under room temperatures, and also during a final period indoors after being outside. During the period of exposure to low temperatures these rats showed lengthened oestrous cycles (average 8.6 days). The length of the cycles varied roughly with the environmental temperature. These

results are interpreted as being due both to the direct effect of temperature on ovarian activity and to the lowered general metabolism of these rats, shown by lowered body temperature and lessened activity. It seems likely that in a state of nature the oestral rhythm may vary considerably with the environmental temperature. The body temperature of the rats varied from 31° C. to 38° C., depending on the environmental temperatures.

—Author's Abstract.

**Studies on the internal secretions of the ovary. I. The distribution in the ovary of the oestrus-producing hormone.** Parkes (A. S.) & Bellerby (C. W.), *J. Physiol. (Lond.)*, 1926, **61**, 562-575.

Extracts of various ovarian tissues from the cow, pig and horse were measured for activity in mouse units. In 5 of 8 cases residual tissue had a greater activity than the corresponding liquor folliculi, while in the remaining 3 cases the liquor folliculi had a greater weight for weight activity. There appears to be some correlation between the size of the follicles and the relative activity of liquor folliculi and residual tissues.—E. Allen.

**Estrus in parabiosis.** Pfeiffer (H.) & Zacherl (H.), *Klin. Wchnschr. (Berl.)*, 1926, **5**, 1522; Abst. *J. Am. M. Ass.*, **87**, 1598.

Pfeiffer and Zacherl made parabiosis experiments on rats. They found that the estrual cycles of two united females are independent. Even pregnancy and lactation of one partner does not influence the cycle in the other. Only in parabiosis of a female with a male did the estrus disappear.

**Clinical tests of ovarian follicular hormone.** Pratt (J. P.) & Allen (E), *J. Am. M. Ass. (Chicago)*, 1926, **86**, 1964-1968; Abst. *A. M. A.*

The effects of injection of ovarian and placental extracts into monkeys, as noted by Pratt and Allen, were as follows: The ovarian follicular hormone starts the periodic growth processes in the female genital tract. In case ovulation occurs, the corpus luteum in woman, and perhaps in other primates, may continue this anabolic endocrine influence, which probably decreases as the next menses approach. Menstruation seems to be partly due to the temporary absence of this secretion after it has been acting for a certain time. But since ovulation followed by corpus luteum formation often does not occur, a specific secretion of the corpus luteum is not a necessary causal factor in the menstrual cycle. That the corpus luteum may possibly have a regulatory influence is not questioned. This substance or a very similar one is probably secreted by, or stored in, the placenta. Its continuous availability throughout the gestation period would account for the absence of menstruation dur-

ing pregnancy. Clinical tests on humans were also made. The ovarian follicular hormone injected into patients represented two kinds of preparations. Both were begun by extracting follicular fluid with lipoid solvents. One was watery emulsion, the other an oil solution of residues. The potency of these extracts was tested before their clinical use by injections into spayed rats. This material was injected subcutaneously in the deltoid region. Although there are many differences between the menstrual cycle of primates and the estrous cycle of other animals, there is one thing common to all, and that is the periodic growth and regression of the uterus in response to stimulation from the ovaries. In primates this regression is accompanied by the menstrual flow, in other mammals it is not. In order to test the action of the follicular hormone on the human cycle, suitable individuals have been selected from time to time. The following groups have been chosen: 1. Artificial menopause. 2. Natural menopause. 3. Primary amenorrhea. 4. Scanty menstruation. 5. Immaturity. The observations made in these cases are summarized as follows: Injections of ovarian follicular hormone into primates, monkeys and human beings, from which ovaries have been previously removed, produce growth in the uterus. Removal of the ovarian follicular hormone by oophorectomy or cessation of injections brings on menstruation in monkeys. Uterine growth and accompanying subjective symptoms similar to those previously experienced at time of menstruation have resulted from injections into patients whose ovaries have been previously removed. No bleeding approximating that of normal menstruation has as yet appeared in women. In one case of scanty and irregular menses in which the ovaries were still intact, a definite increase in flow and regularity has resulted from injection of the hormone.

**Testicular fluid obtained after the method of N. P. Krawkow.**  
Ssentyurin (B. S.), *Ztschr. f. d. ges. exper. Med. (Berl.)*, 1926,  
**48**, 712-723; *Abst. Chem. Absts.*, 1926, **20**, 3183.

Testicular fluid obtained by passing Ringer-Locke solution through isolated testicles of the ox and horse exerts an inhibiting effect on the retrogression of secondary sex characteristics in castrated fowl. The testicular fluid has the power to decolorize dyes of the rosaniline group and the rapidity of the decolorization runs parallel with the physiological activity of the testicular fluid.

**Study of an early human ovum and the functional similarity of the ovarian and placental "hormones."** Young (J.), *Edin. M. J.*, 1926, **33** (Trans. Edinburgh Obstetrical Soc.), 113-125.

Subject matter covered by title.—J. C. D.

**The functional relationship between the pituitary body and the tuber centers.** Collin (R.), Ann. de méd. (Par.), 1925, 18, 428; Abst. Arch. Neurol. & Psychiat., 16, 495.

The connection between the hypophysis and the tuber cinereum is not only nervous—myelinated fibers running within the infundibulum—but also hormonic. Collins has shown that the colloid of the middle lobe of the hypophysis can also be demonstrated in the infundibulum and in the perivascular spaces of the tuber cinereum. He emphasizes that the vegetative centers of this region are under the regulating influence of the hypophysis hormone and do not act as independently as recent publications suggest. In his opinion the overestimation of these vegetative centers without taking into consideration their correlation with the hypophysis will prove as one-sided as was the former endocrinologic point of view.

**Demonstration of hypophyseal secretion in human cerebrospinal fluid taken from the cisterna magna.** Janossy (G.) & Horvath (B.), Orvosi hetil (Budapest), 1925, 69, 1033; Abst. Am. J. Dis Child., 1926, 32, 605.

Before this, only animal experimentation proved that the secretion of the posterior lobe of the hypophyseal gland is always present in the cerebrospinal fluid. The authors used virginal uteri of rats for their experiments, and cerebrospinal fluid taken by cisterna or lumbar puncture. They found that the contraction of the uterus was always much stronger with cerebrospinal fluid of the cisterna puncture than that of the lumbar puncture. Their conclusion is that the secretion of the posterior lobe of the hypophysis reaches the cerebrospinal fluid through the infundibulum, and is diluted and partly reabsorbed in the subarachnoidal space.

**The rôle of the hypophysis in infantile dystrophies.** Lereboullet (P.), Ann. de méd. (Par.), 1925, 18, 452; Abst. Am. J. Dis. Child., 1926, 32, 600.

This is a critical review of recent literature. The so-called hypophysis syndromes in children are often produced by lesions of hypothalmic nuclei. Only gigantism and acromegaly may now be considered as pituitary diseases.

**The anti-diuretic action of pituitary.** McFarlane (A.), J. Pharmacop. & Exper. Therap. (Balt.), 1926, 28, 177-207.

Unanaesthetized dogs were given large quantities of water (400 c.c.) by stomach tube, followed immediately by subcutaneous injection of 1 c.c. of pituitary fluid, with the result that diuresis was inhibited for 4 to 5 hours, during which there was an increase in urinary NaCl. Anti-diuresis was not effected by splanchnic sec-

tion but was overcome by oral administration of 1.5% NaCl or 5% urea solution. If no water was given pituitary produced fleeting diuresis followed by lessened secretion. Water diuresis could not be produced in etherized animals, possibly because of delayed emptying of the stomach due to pulorispasm. Injection of water directly into the gut often failed to produce diuresis, and when it occurred it could not be inhibited by pituitary. The same was true in decerebrate cats. In etherized animals, pituitary injection is followed by a short period of suppression with a subsequent diuresis of short duration. Under anaesthesia, intravenous injection of NaCl or Na<sub>2</sub>SO<sub>4</sub> produced diuresis which was not inhibited by pituitary. The author believes that pituitary accelerates resorption from tubules by direct action on tubular cells and not by any vascular change. The results under anaesthesia were attributed to changes in water distribution in the tissues. The nature of the pituitary fluid used is not stated.—C. I. R.

**The functions of the region of the infundibulum and the tuber cinereum and their relations to the hypophysis.** Roussy (G.), Ann. de méd. (Par.), 1925, 18, 407; Abst. Am. J. Dis. Child., 1926, 32, 569.

Many physiological functions which were attributed to the internal secretion of the hypophysis are now considered as being dependent on centers surrounding the third ventricle. In his experiments on 149 dogs and 46 cats, Roussy has checked up earlier publications and has found new facts, which support the following conception of the role of the vegetative centers of the region of the tuber cinereum: The paraventricular nuclei contain a center for the regulation of the water metabolism; their artificial lesion produces polyuria and transient glycosuria. Other tuber nuclei regulate the fat metabolism; their lesion is followed by Froehlich's syndromes, which could not be produced merely by removing the hypophysis without a lesion of the tuber cinereum. The only function now attributed to the hypophysis (its anterior lobe) is the regulation of the growth of the skeleton, which could not be influenced by artificial lesions of the tuber region.

**The effect of the acidity of the solvent on the stability of the active principle of the infundibulum.** Stasiak (A.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, 28, 1-8.

An investigation of the stability of oxytocic activity. The author reports that infundibular extracts prepared by quickly boiling and fractional sterilization, with acetic acid in varying concentrations with pH ranging from 7.0 to 3.4 showed no loss of activity. Similar extracts prepared with hydrochloric acid with pH=2.6 showed 90% deterioration, but HCL at pH of 4.6 showed no deteri-

oration as compared to standard pituitary preparation (Smith and McClosky). Extracts made by either method when treated with alkali lost all activity, hence the author concludes that there is no appreciable histamin formation. He further concludes deterioration is not a function of the nature of the acid, but more probably of the pH.—C. I. R.

**Fatty atrophy from injections of insulin.** Barborka (C. J.), J. Am. M. Ass. (Chicago), 1926, 87, 1646-1647.

In two cases it was found that localized atrophy of subcutaneous fat may occur at the site of repeated injections of insulin. By varying the site of injection frequently and taking pains to spread the injected fluid widely, it may be possible to avoid such lesions.

—Author's Summary.

**The effect of insulin on the dextrose consumption of perfused skeletal muscle.** Best (C. H.), Proc. Roy. Soc. (Lond.), 1926, 99B, 375-382.

Though several workers previously have presented some evidence that insulin accelerates the rate of disappearance of dextrose in perfusion experiments, the work was repeated with a more efficient apparatus. The perfusion apparatus of Burns and Dale (Jour. of Physiol., in press) was used. There were three experiments in which the hind quarters of cats were perfused with defibrinated blood to which dextrose and insulin were added. In the first experiment the weight of the perfused tissue was 1248 g. The hour before insulin 376 mg. of glucose disappeared, while in the hour after insulin was added 643 mg. disappeared. During the second experiment 620 g. of glucose disappeared as against 324 mg. the hour before. The tissue weighed 652 g. With 728 g. of tissue in the third experiment 324 mg. of glucose disappeared in the hour before insulin, as compared with 620 mg. in the hour after the addition of insulin. The rate of the disappearance of glucose is more rapid after insulin has been added. There was very little disappearance of sugar when the tissue was eliminated from the circulation. The removal of the glucose from the blood used for the perfusion was dependent on the metabolic activity of the skeletal muscles.—E. Larson.

**The influence of ions on the effect of insulin on deoxidizable urine carbon.** Bickel (A.) & Kauffmann, München. med. Wchnschr., 72, 976; Chem. Zentr, 1925, 2, 1182; Abst. Chem. Absts., 1926, 20, 2189.

Experiments indicate that insulin is active under normal conditions only when the body has available a definite mixture of mineral

substances. The action of insulin is therefore closely related to the action of ions. The action of the insulin is located at the boundary surfaces of the cells and metabolic disturbances in diabetes consist partially at least in the inability of sugar to penetrate the cells in sufficient quantity. The increased elimination of mineral substances in avitaminosis is suppressed by insulin, and in general the less the carbon eliminated, the smaller the amount of salts eliminated.

**Effect of insulin and pituitary extract on gastric secretion.** Cascao de Anciaes (J. H.), *Compt. rend. Soc. de biol. (Par.)*, 1926, **95**, 313; *Abst. J. Am. M. Ass.*, **87**, 1516.

Ten persons, healthy or with a stomach disease, were given insulin before a test meal. In seven cases there was an increase of the hydrochloric acid paralleling that of the total acidity. The phenomenon was manifest within the second hour after the meal, and most pronounced in those with gastric neurosis of the hypervagotonic type. An increased gastric secretion appeared before an exaggerated appetite. Evidently the action of insulin is not psychic but exerts its influence on the vegetative nervous system. Thus the fact that many emaciated persons gain in weight under insulin treatment may be explained by the frequency of neurosis of the vegetative type in these patients. Pituitary extract reduced the acid secretion, also apparently through action on the vegetative system.

**Insulin in treatment of denutrition.** Coro (A. J.), *Rev. de med. y ciruj. de la Habana*, 1926, **31**, 373-378; *Abst. J. Am. M. Ass.*, **87**, 1520.

Coro's experience in ten cases has confirmed the prompt benefit and gain in weight experienced under small doses of insulin (3 to 10 units) in extreme denutrition in children and adults, rebellious to repose and forced feeding. The weight increased from 74 to 86 pounds in two months in a girl aged 11, and from 90 to 102 pounds in one month in one young woman—a total of six and five injections.

**Edemas and insulin.** da Fonseca (F.), *Compt. rend. Soc. de biol. (Par.)*, 1926, **95**, 343; *Abst. J. Am. M. Ass.*, **87**, 1516.

Five patients with edema, three of renal origin, were given the same diet and the same amount of liquids, with and without insulin. In these cases da Fonseca found that the amount of the urine was increased under the influence of insulin.

**Experiments on diabetes and insulin action. IV. Inhibition of glucose uptake by the erythrocytes through diabetic plasma (Untersuchungen über Diabetes und Insulinwirkung. IV. Ueber Hemmung der Glucoseaufnahme von seiten der Erythrocyten durch**

diabetisches Plasma). Häusler (H.), Arch. f. d. ges. Physiol. (Berl.), 1926, 213, 602-615.

Erythrocytes take up on the average 30 per cent less glucose from the plasma of adrenaline-diabetic rabbits and of diabetic men than from that of non-diabetics.—A. T. C.

The effect of exercise on insulin action in diabetes. Lawrence (R. D.), Brit. M. J. (Lond.), 1926, 1, 648.

The clinical results of two cases of diabetes mellitus as influenced by exercise were considered. That exercise would reduce glycosuria and blood sugar in diabetes mellitus has been known for many years. The first patient led a sedentary life during the week, but played tennis on Sunday. During the week 16 units of insulin were needed to keep his urine sugar free and reduce his blood sugar to 0.1%. When three or four sets of tennis were played only eight units were required. The second patient was a gardener who, during the fall and winter months, was receiving 10 units of insulin in the morning and 6 units in the evening. In the spring and summer when the most work was done as well as playing cricket in the evening, only 6 units of insulin were required. The immediate effect of exercise is to increase the fall of blood sugar caused by the insulin, but this action only occurs during the maximum period of activity of the insulin (1-4 hrs. after injection). The author concludes that exercise not only increases the power of activity of circulating insulin, but actually causes sugar to be burned which depletes the carbohydrate stores of the body. With the increase of exercise the amount of insulin should be reduced. The patients on insulin treatment should learn to decrease the amount of insulin before unaccustomed exercise.—E. Larson.

On the inverse change between the concentration of glucose and chloride in the blood. Ni (T. G.), Am. J. Physiol. (Balt.), 1926, 78, 158-167.

Histamine causes in dogs a fall of blood chloride (consequent on gastric secretion) which is frequently accompanied by a rise in sugar. This inverse change is more marked in the plasma than in the corpuscles. Similar inverse changes may also be obtained by means of sham-feeding or by partial obstructions of the intestines, although the inverse relationship is not in invariable proportion. Either denervation of the adrenal glands or double adrenalectomy prevents the rise in blood sugar by histamine, without materially affecting the fall in chloride. After total extirpation of the pancreas, the subsequent hyperglycemia is accompanied by a marked lowering of the blood chlorides. An injection of insulin, which brings the sugar down, raises the blood chloride, in diabetic

as well as in non-diabetic dogs. Our results would suggest that while the increase in the blood sugar which accompanied a primary decrease in chlorides is probably the result of reflex stimulation of the adrenals, i. e., the sugar change is not dependent on the chloride, the fall and the rise of blood chloride which occurs in pancreatectomized dogs, or normal dogs after the injection of insulin (primary movement of sugar), are directly related to the sugar fluctuations and may be due to an effort at osmotic and other compensations.—Author's summary.

**An address on diabetes.** Rabinowitch (I. M.), *Canad. M. Ass. J.* (Montreal), 1926, **16**, 1021-1028.

A general review chiefly from the clinical standpoint.

—A. T. C.

**Hypoglycemic coma due to repeated insulin overdosage.** Sevrings-  
haus (E. L.), *Am. J. M. Sc. (Phila.)*, 1926, **172**, 573-580.

The clinical observations made on five patients who had unusual psychic reactions to repeated overdoses of insulin are given. The important findings are amnesia, disorientation, aphasia and sleepiness. The depression was so complete and with such inadequate premonition that in one case a gastric disturbance caused vomiting and a fatal aspiration pneumonia. These unusual reactions were observed only in cases where hypoglycemia occurred at such short intervals within a day that there was little opportunity to replenish glycogen stores. The danger of depending on sugar intake by mouth when gastric stasis may be a complication of the diabetic picture is evident.—Author's Abstract.

**An unusual blood sugar finding during an insulin reaction.** Smith (M.), *Boston M. & S. J.*, 1926, **195**, 663-664.

The blood sugar reading by the Folin and Wu method was zero.—J. C. D.

**The effect of insulin on the respiratory exchange of decerebrate and decapitate cats.** Taylor (A. C.) & Olmsted (J. M. D.), *Am. J. Physiol. (Balt.)*, 1926, **78**, 17-27.

In a decerebrate cat injected with insulin, in which there were no complications through respiratory distress, the respiratory quotient rose, but the  $O_2$  consumption remained level until just before convulsions, when it fell. After a series of convulsions the respiration fell, while the  $O_2$  consumption and ventilation rose. In decapitate cats injected with insulin, the  $O_2$  consumption generally falls temporarily either just before or at the time when hypersensitivity is observed. A rise in  $O_2$  consumption is usually associated with muscle spasms. The respiratory quotient shows a definite rise

to a maximum immediately before convulsions. During convulsions there is a fall in the respiratory quotient. The severity of symptoms is associated with the magnitude in the changes in the respiratory quotient. In decapitate cats injected with curare and insulin the changes in  $O_2$  consumption show variations which do not follow any definite rule. The most striking change is the rise in respiratory quotient nearly to unity. When the caloric output is calculated it is found that the total metabolism does not change in any marked degree except when convulsions occur. There is usually a fall in the caloric output just before the convulsions. The proportion of the caloric output due to combustion of carbohydrate, however, rises from zero or a low level, until just before time for convulsions it often accounts for the total caloric output. The same marked rise in the proportion of the caloric output due to carbohydrate combustion is seen following the injection of insulin in the curarized animals.—Author's Abstract.

**The antagonistic action of insulin and hypophysis upon water economy (Die antagonistic wirkung des insulins und hypophysen hormons auf den wasserhaushalt).** Vollmer (H.) & Serebrijski (I.), Biochem. Ztschr. (Berl.), 1925, 164, 1.

Pituglandol and insulin each has an antidiuretic action separately, but when given in combination produces lesser water retention than with pituglandol alone. The authors think that insulin hinders the action of pituitary, especially the renal components of this action, the blocking of the kidneys. With simultaneous action of both hormones, the blood dilution fails to appear. Primarily the water imbibed during the experiment is stored in the tissues and, as soon as the hormone effect is gone, the tissue water enters the blood vessels and then acts as a stimulant on the kidneys. The inhibiting effect of the insulin on pituitary can be explained on a central basis. The experiments consisted of administering 1500 c.c. of water to patients and then examining the urine every hour for specific gravity, amount passed, and sodium chloride content, while the blood was examined for concentration, serum protein and hemoglobin content. Pituglandol was injected at the beginning of the experiment and two hours later. Insulin was injected on the third day and insulin and pituglandol later.—M. B. Gordon.

**Regulation of metabolism. II. The incretory regulation of fat mobilization (Stoffwechselregulationen. II. Die inkretorische Regulation der Fettmobilisierung).** Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, 213, 280-286.

Insulin inhibits peripheral fat mobilization in all cases, as for example after phloridzin administration. With strong doses of insulin the inhibition may be complete. No transference of fat to the

liver takes place. Adrenaline produces similar effects only in heavy doses, and never completely.—A. T. C.

**Regulation of metabolism.** III. Nervous and incretory influence on fat changes in the liver (Stoffwechselregulationen. III. Der nervöse und inkretorische Einfluss auf die Umwandlung von Fett in der Leber). Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, 213, 287-297.

Insulin accelerates fat change in the liver; at the same time glycogen increases. Also after adrenaline dosage there is rapid fat degradation and formation of glycogen in the liver.—A. T. C.

**Regulation of metabolism.** IV. The incretory influence on change of fat into carbohydrate in the liver (Stoffwechselregulationen. IV. Die inkretorische Beeinflussung der Umwandlung von Fett in Kohlenhydrate in der Leber). Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, 213, 298-320.

Dogs that after phloridzin treatment are depleted of sugar and whose livers contain but traces of glycogen, but much fat, are much less sensitive to insulin than are dogs that have been for the same period starved or fed a normal diet. Symptoms of insulin-poisoning appear with each, but weaker with the former, who rapidly recover. There is a corresponding lowering of the blood sugar curve with each, but a more rapid after-rise with the phloridzin animals. These show marked depletion of the liver fat, with formation of fresh glycogen, indicating formation of carbohydrate from fat in the liver under the accelerating action of insulin. In the control animals there is no such possibility of formation of sugar from fat; insulin inhibits mobilization of peripheral fat depots. Similar phloridzinised dogs show more marked reaction to adrenine than do normal animals; adrenine also accelerates the change from fat to carbohydrate.—A. T. C.

**Interesting results from use of parathyroid extract in case of osteitis deformans (Paget's disease).** Bassler (A.), J. Am. M. Ass. (Chicago), 1926, 87, 96-97; Abst. A. M. A.

Suggested by the work of Collip on parathyroidectomized dogs in which the administration of extracts of parathyroid glands raised the calcium content of the blood, this substance was employed by the author in a case of osteitis deformans with a happy result. In this case of steadily progressing Paget's disease no treatment was of any value up to the moment the parathyroid was started. Within a short time after its use was established a most marked change for the better occurred. The dose of parathyroid was 1/10 grain (0.006 gm.) after each meal.

**Changes in the chemical and physical characteristics of the blood following the administration of parathyroid hormone.** Cantarow (A.), Caven (W. R.), & Gordon (B.), Arch. Int. Med. (Chicago), 1926, 38, 502-509.

In a study of ten clinical cases of pulmonary tuberculosis it was found that there seemed to be no significant change in carbon dioxide combining power or in the plasma chlorides following the administration of parathyroid hormone. There was a tendency toward increased concentration of the blood as evidenced by an increase in red and white counts, hemoglobin, and in the blood viscosity. A definite decrease in clotting time was noted in most cases. The time of most rapid coagulation corresponded in every case to the point at which the whole blood calcium was highest, rather than to the highest point of the serum calcium.—R. G. H.

**Therapeutic value of parathyroid hormone.** Collip (J. B.), J. Am. M. Ass. (Chicago), 1926, 87, 908-909; Abst. A. M. A.

Collip states that the function of the parathyroid hormone is in the main related to calcium and phosphorus metabolism. It is possible that the parathyroid glands subserve other functions, and it is also possible that there may be other hormones in these glands of which we have no knowledge at present. Experimental parathyroid tetany is characterized by a lowered calcium content of the blood serum and as a rule an increase in the inorganic phosphorus. The parathyroid hormone, when administered by injection to dogs in a state of parathyroid tetany, causes the blood calcium level to be restored and the inorganic phosphorus if increased to be decreased. There is also the restoration of the animal to an apparently normal condition. There is also noted a definite quantitative relationship between the dosage administered and the calcium mobilizing effect produced. Normal dogs which have been injected with an active parathyroid extract manifest an increase in the blood serum calcium which is proportionate to the dosage administered. Overdosage effects which may result in death have been produced consistently in both normal and parathyroidectomized dogs. The main physiologic action of the parathyroid hormone as seen by the laboratory worker is that of a blood calcium mobilizer. It would therefore seem logical to conclude that the parathyroid hormone will be of definite therapeutic value in any condition in which the blood serum calcium is below the normal value. Blood serum calcium has been shown to be lowered in post-operative tetany, in spasmophilia, intropical sprue and in certain types of nephritis. Collip suggests to clinicians that a potent parathyroid extract is now available which has the specific effect of mobilizing calcium in the blood stream. If one is desirous of influencing profoundly calcium metabolism, the new hormone may be employed as the therapeutic agent.

**Studies on the pathogenesis of tetany. VII. The prevention and control of parathyroid tetany by the oral administration of kaolin.**  
Dragstedt (L. R.) & Sudan (A. C.), Am. J. Physiol. (Balt.), 1926,  
77, 314-319.

The oral administration of kaolin in amounts of from 50 to 200 grams was found to be effective in controlling parathyroid tetany and in preserving the life of completely thyro-parathyroid-ectomized dogs. It is suggested that this effect of kaolin is due to the absorption of toxic products of bacterial growth in the gastro-intestinal tract and to the predominance of an aciduric intestinal flora which it brings about. These experiments are interpreted to support the views that parathyroid tetany is an intoxication and that the responsible toxic substances in non-pregnant animals arise chiefly in the gastro-intestinal tract as a result of bacterial proteolysis.—Author's summary.

**The effect of parathroid extract and liver extract on the hypertension produced by guanidine compounds.** Major (R. H.) & Buikstra (C. R.), Johns Hopkins Hosp. Bull. (Balt.), 1925, 37, 392-399.

The authors found that the elevation of blood pressure produced by guanidine compounds was abolished by the use of parathyroid extracts and liver extracts. The parathyroid extracts used were prepared by the method of Hanson and Collip. The liver extract employed was prepared by the method of acid alcohol extraction and alcoholic fractionation. The dose of parathyroid extract and liver extract which produced experimental hypertension had only a slight effect upon normal blood pressure.—R. H. Major.

**A case of sub-parathyroid tetany treated with Collip's extract of parathyroid.** Monteith (J. R.) & Cameron (A. T.), Canad. M. Ass. (Montreal) J., 1926, 16, 1104-1106.

Recurring exophthalmic goitre led to a second thyroidectomy, and though care was taken by the surgeon to conserve sufficient thyroid and parathyroid tissue tetany developed within three or four days of the second operation, and, later on, symptoms of hypothyroidism. The latter was controlled adequately by desiccated thyroid. The former was partially controlled by calcium lactate by mouth, and completely by injections of Collip's extract. Eighty-two days after this operation with withdrawal of the extract and lactate for a sufficient period the serum calcium fell to the low level initially reached indicating that at that period there was no hypertrophy of any parathyroid tissue that remained. Within two months of this date, on calcium lactate therapy alone, apparently such a hypertrophy occurred, since the serum calcium returned to normal,

and discontinuance of the lactate was followed neither by lowering of the serum calcium nor by any clinical symptoms of tetany.

—A. T. C.

**Effect of parathyroid feeding on the thyroid.** Woodman (Dorothy), J. Physiol. (Lond.), 1926, 61, 557-561.

A report of experiments in feeding young and adult rats of both sexes with 0.02 gm. daily of desiccated parathyroid from 2 to 5 weeks. Both the thyroid and parathyroid glands were examined grossly and microscopically. There was no marked change in the parathyroids of rats so fed as compared to those of controls. The thyroids presented an inactive appearance manifested by increased colloid and distended vesicles. The author believes this suggests that the two glands are antagonistic in function, since there were no changes induced resembling those following thyroid feeding as would be the case if the function of the parathyroids is to replace the function of the thyroids.—C. I. Reed.

**Extirpation of the parathyroid gland in the domestic fowl. II. Report.** Yamaoka (H.), Acta scholae med. univ. imp. (Kioto), 1925, 8, 209-240.

The extirpation of parathyroid tissue is followed by a more or less marked increase in the electric excitability of the peripheral motor nerves, although not to the same extent as in the mammalia. As a rule, no alteration of the normal sequence of the various responses results, but the A. O. C. is more marked than the A. C. C. The increased electric excitability of the peripheral nerve is independent of the charge from the central nervous system. It occurs whether the nerve be cut before or after the removal of the parathyroids and persists till degeneration sets in. The electric excitability of muscle to direct stimulation is increased after parathyroidectomy, although not to the same extent as that of the nerve. This is chiefly due to an increased electric excitability of the neural structures in the muscle, since it is generally abolished by a dose of curare sufficient to block nervous impulses. In the disturbance occurring after parathyroidectomy, the increased electric excitability of the peripheral motor nerve is somewhat proportionate to the intensity of the symptoms due to the condition of the central nervous system. The extirpation of the parathyroid gland produced no detectable symptoms of the central nervous system in a large majority of our cases.—Author's abstract.

**Extirpation of the parathyroid gland in the domestic fowl. Third Report.** Yamaoka (H.), Acta scholae med. univ. imp. (Kioto), 1925, 8, 241-263.

The administration of guanidine salts to domestic fowls induces symptoms, which are almost identical with those of tetania

parathyreopriva. At the same time the hyperexcitability of the peripheral nerves, which also occurs after removal of the parathyroid, is induced by the administration of the drug. The hyperexcitability resulting from the lack of the parathyroid, therefore, may be due to the action of guanidine, which is increased in the blood under that condition. After several successive days the electrical excitability decreases again. In fowls, the hyperexcitability of the nervous system produced by guanidine administration is restored by the injection of calcium lactate. As the experiments above described show, the clinical symptoms and electrical hyperexcitability on the peripheral nerves in fowls after the extirpation of the parathyroid, or after the administration of guanidine salts, are slighter and lower than those in mammalia under the same conditions.—Author's abstract.

**The influence of thymus feedings on amphibia and mammals.** Romeis (B.), Klin. Wechschr. (Berl.), (1926), 5, 975-977.

Metamorphosis and subsequent growth in tadpoles was inhibited by feeding a diet made up exclusively of thymus. Controls, fed liver only, did not show this retardation. Similarly one series of young rats were fed only thymus and water while controls were fed liver and water. The thymus-fed rats showed signs of marked inhibition of both growth and development eventually developing cachexia, which was soon terminated by death. The males seemed slightly more susceptible than the females. The controls did not show these changes. There was retardation of bone growth, hypoplasia of the lymphoid tissues and striking involution of the thymus. The changes in the thyroid and hypophysis were less marked. The heart, lungs, spleen, kidneys, and suprarenals were smaller than in the controls. There were very slight differences between the weights of the brains and the skulls of the thymus-fed as compared with the liver-fed rats. The ovaries and testes of the thymus-fed rats showed striking indications of arrested development. In the females the cyclic changes were not seen, while they occurred regularly in the controls of this sex.

It was found that all these changes could be prevented if vitamin-rich vegetables were added to the thymus feedings. The author therefore believes that the inhibitory effects observed were due not to a specific hormone present in thymus tissue, but to a lack of vitamin substances essential for development and growth.

No experimental data are included in the article.—S. Shapiro.

**Diet and action of internal secretions. VI. The action of thyroxine during feeding with diets of different composition (Ernährung und Inkretwirkungen. VI. Thyroxin-Wirkung bei Verfütterung verschieden zusammengesetzter Nahrung).** Abderhalden (E.) &

Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, 213, 328-335.

The action of thyroxine on metabolism depends greatly on diet. Rats fed carbohydrate-rich, protein-poor diet under dosage of thyroxine show but slight (14%) increase in gas-metabolism, which rapidly returns to normal. On protein-rich diet the effect is much greater (an average increase of 37%) and lasts over 9 days. On fat-diet intermediate results are obtained.

**Goiter patient unsuited to thyroidectomy.** Bartlett (W.), J. Am. M. Ass. (Chicago), 1926, 87, 1279-1282; Abst. A. M. A.

There are certain persons who simply cannot be restored to a condition in which thyroidectomy seems advisable. The author divides them into four classes: those who die of thyrotoxicosis; those who are dismissed as hopeless; those who are intolerant of restraint, and those who die of intercurrent diseases. The first class are not saved from death by compound solution of iodine, roentgen-ray treatment injections and ligations. In Bartlett's clinic, six criteria determine the patient's fitness for operation. They refer to heart condition; blood nitrogen; metabolic rate; patient's weight; self-control, and blood pressure. As far as the heart is concerned, there may be transient fibrillation, but there must be no organic congestion and the rate must not be too fast, while the electrocardiogram should conform to ordinary standards. As far as blood nitrogen is concerned, it must be under 50. The metabolic rate should be about 40 plus, although a falling rate of 50 plus is much more desirable than a rising rate of 40 plus. As to regaining of weight, it should be at least 50 per cent of what the patient has lost in order for conditions to be ideal in this particular. The regain of self-control is exemplified in many ways, the best of which is a spirit of cooperation. It is a favorable sign for a patient to urge the operator to continue postponement of the operation as long as his judgment dictates; whereas, on the other hand, the patient who urges him on all occasions to operate is likely to be a victim of a severe postoperative explosion. The blood pressure, in order to be satisfactory, should be fairly high, with a wide pulse pressure even though there is some shading. Bartlett suggests 140/65-55 as being about the average. A low operative mortality can result only from adequate preparation and a correct choice of patients. These two considerations, if any, justify the treatment of goiter as a specialty, much as the treatment of central nervous lesions has become a recognized specialty in surgery.

The elimination of the iodine in the urine in normal patients and in exophthalmic goiter. Cattell (R. B.), Boston M. & S. J., 1926, 195, 69-71.

Normally 70% of the iodine given is excreted in the first 24 hours. In the thyroid cases the elimination is less. The authors suggest that the usual 250 mg. daily dose is excessive for supplying the needs of the thyroid. Tables of excretion are given.—J. C. D.

Specific influence of the thyroid gland on hair growth. Chang (H. C.), Am. J. Physiol. (Balt.), 1926, 77, 562-567.

Albino rats deprived of thyroids show a retardation of hair growth. Upon feeding suitable amounts of thyroid (0.5 to 0.7 gram) in the dose of 0.03 gram per day, hair grows normally. Undernourished animals with intact thyroids show a similar retardation of hair growth. Thyroid feeding to such animals kept on the chronic starvation diet improves the hair growth in spite of the further decreased body weights caused by excessive catabolism in addition to the originally deficient anabolism. This proves the specific influence of the thyroid gland on hair growth. Feeding of thyroid accelerates the hair growth in some normal animals, while in others no such result was obtained. Further experiments are required to determine whether the refractory animals have thyroids functioning at a rate optimum for hair growth. Excessive amount of thyroid given by repeated administrations over a long period of time retards the hair growth of the normal animal due to the secondary nutritional upset of increased catabolism. Further work on the study of the constituents of the thyroid gland responsible for this hair reaction has been in progress in order to determine whether or not this hair reaction can be used as a functional test of the thyroid gland.—Author's abstract.

Nephrosis of thyroid origin. Davidson (J. R.), Canad. M. Ass. J. (Montreal), 1926, 16, 1059-1063.

Three cases are reported, each showing different peculiarities. The first was a case of nephrosis with mild hypothyroidism, which was greatly improved by thyroid treatment, relapsed after cessation of the treatment, and finally was apparently spontaneously cured, the patient now being—as shown by clinical examination—a normal young woman. The second, a case of nephrosis with marked hypothyroidism and hypoparathyroidism, was also greatly benefited by the combined administration of desiccated thyroid and Collip's parathyroid extract, but finally died of an intercurrent infection. The third was a case of hypothyroidism and apparent hyperparathy-

roidism (serum calcium above normal), markedly emaciated, with apparent dehydration of tissues. Under thyroid treatment the basal metabolic rate returned to normal, the patient gained weight, and the serum calcium fell to normal figures. Continued treatment led to a metabolic rate above normal with continued gain of weight. Cessation of thyroid administration did not stop these progressive changes, and in the 18 days thereafter the rate rose from plus 14 to 65 per cent, and the weight increased from 100 to 135 lbs. In the next 28 days the rate fell to plus 24 per cent, but the weight increased to 153 lbs. During this period there was no clinical symptom of hypo- or of hyper-thyroidism, and no pituitary or other explanatory change could be demonstrated. It is suggested that nephrosis associated with pregnancy may also be due to slight thyroid deficiency, and that in this condition small thyroid doses may be of value.—A. T. C.

**Thyroid hypertrophy and pregnancy.** Davis (C. H.), J. Am. M. Ass. (Chicago), 1926, **87**, 1004-1009; Abst. A. M. A.

Approximately 41 per cent of the last 520 women examined by the authors in early pregnancy had visible hypertrophy of the thyroid. Eight of these patients have returned with typical symptoms of toxic goiter within fourteen months after delivery. Small doses of iodine have been administered during pregnancy, but none after delivery. No patient has returned with hyperthyroidism earlier than four months after delivery. Overwork, worry and other forms of nervous strain appear as contributing causes in each case. The use of iodine during pregnancy by women who live in goiter districts is advocated as a prophylactic measure, unless they have adenoma of the thyroid. Iodine hyperthyroidism is recognized as a possibility, but thus far has not been observed. The average metabolic rate of nine women with normal thyroids at term was + 2.4 per cent. Their average after delivery was —1.3 per cent. The average rate of seven women with simple hypertrophy was + 22.1 per cent before term, with a later drop to + 3.1 per cent. The average rate of nine women believed to be of the hyperthyroid type was + 32.2 per cent before delivery, with a drop eleven days post partum to + 8.9 per cent. With the exception of two patients in the last group, these patients took small doses of iodine during the last months of pregnancy. Patients previously operated on for toxic goiter are usually benefited by taking small doses of iodine during pregnancy. One such patient in the small group under observation apparently could not tolerate iodine. One patient had a successful operation for toxic adenoma of the thyroid in the fourth month of pregnancy.

and later took iodine. One patient with a history of toxic adenoma took iodine during pregnancy with apparent benefit, although she had a metabolic rate of + 86 at term. She was successfully operated on twenty days post partum. The baby was continued at the breast, and complementary feedings were stopped six days after the operation. The subsequent history of both mother and infant is very satisfactory. Prolonged nausea and vomiting in one case was evidently due to a crisis of exophthalmic goiter. The metabolic rates on this patient are given. She had a rate of + 81 per cent ten days before delivery. Her nausea was lessened by the use of iodine. Patients with toxemia of pregnancy had low readings. Three with edema and little or no albumin had lower readings than the single patient with high blood pressure, albumin and casts but no edema. Comparative studies of the blood calcium and thyroid function, as indicated by the basal metabolic rate, show no relation between the milligrams of calcium in each hundred cubic centimeters of serum and the metabolic rate. The calcium determinations in twenty-four women with uncomplicated pregnancy showed an average of 9.97 mg. before delivery and 10.5 eleven days post partum. Most of these women had taken calcium salts in addition to their food. The average for the patients with thyroid hypertrophy was slightly higher than the average for the women with normal thyroids, but a small series does not warrant conclusions. Three patients with toxemia of pregnancy showed a lowering of the calcium post partum, while the normal patients usually showed an apparent increase within eleven days. The use of cod liver oil and ultraviolet irradiation did not appear to increase the blood calcium in the few cases studied.

**Thyroid therapy and thyroid tolerance in chronic nephrosis.** Epstein (A. A.), J. Am. M. Ass. (Chicago), 1926, 87, 913-918; Abst. A. M. A.

Epstein calls attention to the enormous tolerance of patients with nephrosis for thyroid substance and thyroxin. He has found that in chronic nephrosis the amount of thyroid or thyroxin necessary to produce a therapeutic effect is most extraordinary. For example, daily doses of from 1 to 4 gm. (15 to 60 grains) of thyroid are often required over long periods of time to elicit a metabolic response. The fate of the thyroid and thyroxin in chronic nephrosis has not been determined by Epstein; whether the unusual tolerance exhibited by these patients is due to increased excretion, inactivation, or lack of absorption by the tissues is still problematic. The problem in the treatment of chronic nephrosis is threefold, namely: (1) To replace the protein loss of the blood plasma which results

from the albuminuria and which plays so large a part in the retention of water and the formation of edema. This is best accomplished by feeding a high protein diet; that is, 2 and 3 gm. of protein per kilogram of body weight. (2) To compel the tissues to utilize protein and incidentally to reduce the lipoidemia. This, too, is often accomplished by a liberal protein, but fat-poor diet. The administration of thyroid aids in attaining this desideratum. (3) To re-establish normal metabolism. When high protein feeding fails to accomplish this, the institution of thyroid is definitely indicated. Epstein's method of treatment is as follows: When the preliminary high protein feeding fails to give any therapeutic result, such as elimination of the edema, control of the albuminuria, and change in the chemical reaction of the blood, the use of thyroid is begun. The initial dose is usually small, from  $\frac{1}{2}$  to 1 grain (0.03 to 0.065 gm.) three times a day. In many instances this dose may be sufficient to enhance the effect of the high protein diet in attaining its therapeutic success. As a rule, however, much larger doses are needed. The amount of thyroid is therefore rapidly increased until a daily dose of 15 grains (1 gm.) is reached. If such a dose fails to give any indication of effectiveness, it is immediately doubled and administered for from five to seven days. If this in turn does not give therapeutic results, the use of thyroxin is resorted to. It is given intravenously, the initial dose being from 5 to 10 mg. This dose may be repeated at intervals of from five to ten days until definite effects are observed. The beneficial effect is indicated by increased diuresis, diminution in the albumin output and decrease in the lipoidemia. While increase in pulse rate and elevation of temperature occasionally follow the use of thyroxin, no toxic symptoms develop as long as the lipoidemia persists. The oral administration of thyroid in large doses occasionally causes gastric distress, such as anorexia and nausea, and in such cases the use of thyroxin is resorted to at once. As soon, however, as therapeutic results are evidenced, the dose of thyroid and thyroxin is reduced, the main guide being the lipoidemia. Thyrotoxic symptoms have not been observed thus far, in spite of the enormous doses of thyroid and thyroxin used, a fact which would seem to indicate that untoward symptoms are not likely to occur prior to a favorable turn in the clinical course of the disease.

**The rôle of the thyroid apparatus in the growth of the reproductive system.** Hammett (F. S.), Am. J. Physiol. (Balt.), 1926, 77, 527-547.

A study is given of the normal course of development of the

reproductive systems of male and female albino rats which serves as a basis of determination of the rôle of the thyroid apparatus therein. An improvement in dietary and environmental conditions brings about an earlier sexual maturity. The reproductive system of the male reaches maturity at an earlier age than does that of the female. The development of the uterus lags behind that of the ovary. The sociological implications of these findings in their relation to man are briefly indicated. There is no apparent specific relation between the growth of the reproductive system of either sex and thyroid or parathyroid activity. The growth retardation which occurs is attributable to the general metabolic disturbance which results in a condition of essential undernutrition, and the dependence of the parts of the body on the effectiveness of the growth processes of the whole. The ovary and the uterus follow the body weight in its changes in growth retardation after glandular removal at the stated ages. The degree of retardation is of the same order of magnitude until the practical completion of the pubertal adjustment, when the surge in ovarian incretory activity determines a relatively increased sensitivity of the reproductive system. This is evidence for an ovary-thyroid and ovary-parathyroid incretory relationship, the basis of which lies in the ovary. Evidence is had that the incretory activity of the ovary conditions the response of the uterus to the glandular deficiencies, when and only when, the latter has reached the period in which it attains its full functional maturity. The testis and epididymis are less sensitive to thyroid and parathyroid deficiency than is the body as a whole. Prior to the pubertal adjustment they do not follow the body weight change with change in age at time of glandular removal. After the readjustment they show a direction of change like that of the body. The difference is attributable to a difference in the relative proportion of total growth represented by growth by increase in cell number. The pubertal adjustment decreases this difference and hence the growth reaction of the reproductive system approximates in kind that of the body as a whole. The marked concordance of testis and epididymis response both in degree and kind is attributable to the close functional and structural association between the two. The relations outlined are consistent with the pertinent coefficients of correlation. Evidence is had that a factor in the greater incidence of thyroid disturbances in girls and women as compared with boys and men, is the presence of a greater incretory relation between ovary and thyroid, than is evident between testis and thyroid. The relations of the growth responses of the various organs to those of the body as a whole and to each other, subsequent to glandular removal at the different ages, confirm the belief as to the

rôle of the thyroid apparatus in growth developed in an earlier study.—Author's abstract.

**Exophthalmic goiter in childhood.** Helmholz (H. J.), J. Am. M. Ass. (Chicago), 1926, 87, 157-162; Abst. A. M. A.

Thirty cases of exophthalmic goiter occurring in children less than 15 years old are reviewed by Helmholz. Compound solution of iodine, administered in doses of from 5 to 10 minims (0.3 to 0.6 cc.) three times a day, reduced the basal metabolic rates and toxic symptoms very markedly. It made preliminary operations unnecessary in the last eleven cases. Of twenty-four patients operated on, two died, one in crisis twenty-four hours after operation and the other from bronchopneumonia one week after operation. The duration of the symptoms, which varied from six months to eight years, indicates that frequently this disease is not recognized early or its seriousness is not appreciated. The patients came largely from Minnesota, Iowa, Illinois and Wisconsin, in the order named. Tachycardia was noted in 100 per cent of the cases. The thyroid gland was definitely enlarged in all but two cases. All but two patients complained of nervousness. Emotional instability was perhaps the most marked feature. Exophthalmos was definite in twenty-five of the thirty cases, and in one of the remaining five there was the characteristic stare.

**Goitre in children—a study of treatment.** Kitchen (H. D.), Canad. M. Ass. J. (Montreal), 1926, 16, 923-931.

Three groups each of 24 children with goitre were treated respectively with desiccated thyroid (1 to 2 grains per day), Lugol's solution, and expectantly. After from three to six months' observations the following conclusions are drawn (it has been noted that the amount of improvement obtained in the first three months of treatment indicates the degree of result to be obtained by a further continuation of therapy): Desiccated thyroid produced a greater number of marked improvements and less failures than did iodine (Lugol's solution) or the expectant therapy. Iodine treatment produced much better results than those occurring in the untreated cases. No cases of iodine hyperthyroidism resulted from the use of Lugol's solution, and continuous use of desiccated thyroid produced no untoward effects. The necessity of frequent examination of the patient on thyroid treatment is insisted on though clinical observation is sufficient and frequent basal metabolic rate determinations are not necessary.—A. T. C.

**Quadriceps test for myasthenia of thyroidism.** Lahey (F. H.), J. Am. M. Ass. (Chicago), 1926, 87, 754; Abst. A. M. A.

A test is described by Lahey which is said to be of considerable value in diagnosis of hyperthyroidism based on the well established weakness of the quadriceps femoris in this disease. The patient sits well forward on the edge of a straight chair and holds the leg out at right angles to the body. In very few cases of thyroidism of any marked degree of intensity will it be possible for one to maintain the leg in this position more than twenty-five or thirty seconds, while in the majority of cases not affected by thyroidism the leg can, with any real effort, be held in this position for approximately one minute.

**Substernal goiter.** Lahey (F. H.), J. Am. M. Ass. (Chicago), 1926, 87, 1282-1286; Abst. A. M. A.

The author contends that any tendency for a goiter to become substernal is an indication for its removal. The ill effects of substernal goiter are primarily deviation, flattening, and narrowing of the trachea. The diagnosis by means of roentgen-ray and physical examination may be made with considerable certainty. Surgical removal may be accomplished in a great majority of cases even when the substernal mass has passed downward behind the arch of the aorta, but an operative procedure of this magnitude would be unnecessary if the early adenomas and cysts were removed while still only tending to become intrathoracic. In an experience with more than 200 substernal goiters, Lahey has succeeded in accomplishing their removal without removal of the manubrium in all except two cases. The technical features of removal of substernal goiters are the prevention of hemorrhage and the protection of the pleura, thoracic duct, and recurrent laryngeal nerve, three structures which form the walls from which the intrathoracic mass must be separated, the prevention of tracheal collapse, and insufficient air intake during removal and the extrication of the mass. These steps may all be accomplished by gentle manipulations in the proper lines of cleavage and with the cooperation of an anesthetist experienced in the methods of aiding these patients in getting air during the time tracheal pressure is being made during the manipulative removal of the mass. This has been accomplished by a tight mask and the introduction of oxygen into the lungs by pressure.

**Myxedema simulating pernicious anemia.** Meulengracht (E.), Ugesk. f. Laeger (Copenhagen), 1926, 88, 721; Abst. J. Am. M. Ass., 1926, 87, 1252.

Meulengracht's patient was a young woman presenting the clinical picture of chronic pernicious anemia with a rather torpid course. The basal metabolism was found 40% below normal, and, under thyroid treatment recovery was prompt and complete. The slight tendency to a myxedema aspect had not been recognized until the basal metabolism had given the clue. The achylia, blood changes, paresthesias and leukopenia observed are common to both pernicious anemia and thyroid deficiency.

**Pregnancy complicating exophthalmic goiter.** Mussey (D.), Plummer (W. A.) & Boothby (W. M.), J. Am. M. Ass. (Chicago), 1926, 87, 1009-1011; Abst. A. M. A.

To elucidate the question of a possible relationship between exophthalmic goiter and adenomatous goiter with hyperthyroidism and pregnancy, as well as to determine their clinical effect on one another, a study has been made by the authors of forty-two women whose pregnancy was complicated by these diseases. There was no evidence that pregnancy influenced the course of exophthalmic goiter. Serious additional complications were not more frequent than is usual in either condition alone, and therapeutic abortion was not necessary. Both the course of pregnancy and the maternal and fetal mortality were not appreciably affected as the result of the syndrome due to exophthalmic goiter or to adenomatous goiter with hyperthyroidism, nor, on the other hand, did the pregnancy render the control of these two diseases noticeably more difficult.

**The influence of anxiety states on the thyroid gland.** Newburgh (L. H.) & Camp (C. D.), Am. Clin. Med. (Balt.), 1926, 4, 1006-1011.

Abnormalities other than lesions of the pancreas are capable of disturbing the carbohydrate metabolism. The following case record shows how a mental disturbance may upset the metabolism of carbohydrate in such a way as to simulate diabetes mellitus.

Case record: Patient complained of the usual diabetic symptoms, and in addition a variety of pains and nervousness. Progressive loss of memory was noted. For two years there was palpitation, shortness of breath and precordial pain. Urine, on non-restricted diet, contained glucose. Glucose tolerance test gave the following readings:

Fasting .....	0.100 per cent
First hour .....	0.232 per cent
Second hour .....	0.242 per cent
Third hour .....	0.188 per cent

Physical examination was negative except for very slight enlargement of the thyroid gland. Pulse rate 106. She was given the usual diabetic treatment and discharged on a diet yielding 2200 calories, with a total glucose value of 90 grams. She remained sugar-free four months and gained weight, but returned complaining of more fatigue and increase in her nervous disturbances. She had recently had several severe attacks of palpitation and choking, ending in unconsciousness. Her condition suggested toxic adenoma, and this suggestion was borne out by four determinations of the basal metabolic rate, with the following readings: 20, 38, 36 and 35 per cent above normal, but she did not show exophthalmos, tremor or definite palpable abnormalities of the thyroid gland. She was subjected to psycho-analysis. It was found that the seizures of which the patient complained were thought by her to indicate diabetic coma and approaching death. During her late girlhood she was compelled to remain away from school to nurse her sick mother. During this time an episode had occurred which the patient feared would cause her mother's death. Subsequent death of her mother increased the emotion. She finally succeeded in repressing this extremely painful thought, and was apparently quite well until another emotional conflict arose shortly before she began having symptoms four years ago. The conflict involved an ethical question and was associated with the former effect. When a doctor told her that she had diabetes she had a basis to transfer her anxiety to her own health, thus further covering up the original cause of the trouble. She was easily convinced that she could not have been the cause of her mother's death, and during this period her metabolic rate gradually fell to -4%. Since then it has been normal. She was placed on a non-restricted diet and the urine remained sugar-free. Her glucose tolerance curve at this time showed:

Fasting .....	0.083 per cent
After one hour.....	0.157 per cent
Two hours .....	0.108 per cent
Three hours .....	0.077 per cent

We have, therefore, in this case a demonstration that emotional disturbance may produce the standard picture of diabetes mellitus, with its large appetite, loss of weight, weakness, glycosuria and characteristic tolerance curve. The change in the glucose tolerance curve is especially impressive and suggestive.

—Author's Abst.

The chemical and histo-pathological changes in the thyroid in different diseases incident to men (Ueber die chemischen und patholo-

gisch-histologischen Veränderung der Schilddrüse bei den verschiedenen Erkrankungen des Menschen). Nosaka (T.), *Folia Endocrinol. Jap.* (Kyoto), 1926, Bd. II, s. 2.

Determinations carried out by the Bauman-Anton method showed equal distribution of iodine in different parts of the gland with a gradual increase with age from the embryo to middle life, except for a sudden rise at puberty. After middle age there is a gradual decrease, and generally an atrophy of the gland after the sixtieth year. The weight of the thyroid in the Japanese is much less than in Europeans, but with the iodine content exactly the reverse is true. In pulmonary tuberculosis, tetanus, suppurative inflammation, and uremia there is an increase in iodine and gland weight. In Basedow's and Addison's diseases, acute infections such as enteric fever and miliary tuberculosis, beri-beri and gastric ulcer, there is an increase in gland weight or iodine content, or both. Diabetes, status lymphaticus, icterus and cancer cachexia (except in breast or neck locus) have no definite relation to weight of the thyroid or the iodine content.—E. P. Durrant.

**Goitre incidence in New Jersey school children.** Reichle (H. S.), *Arch. Ped.* (N. Y.), 1926, 43, 329-334.

In the city of Irvington, 2150 children between the ages of 6 to 17 years were examined. Enlarged thyroids were found in 14.7 per cent of the girls and in 3.5 per cent of the boys. There was a marked rise at 9 to 11 years of age, with a drop following this period, and a subsequent rise at the ages of 16 to 17 years. It is logical to assume that the increase between 9 and 11 years is due to influence of adolescence. More factors than iodine content are involved. The thyroid enlargements are purely relative and depend not only on actual hypertrophy of the gland but also on the size and contour of the individual neck. It is obvious that the mensuration of thyroid is quite faulty. It does not seem probable that iodine medication in schools before or during adolescence could reduce the percentage of these physiological goitre of non-goitre districts. No reduction in the size of adolescent goitres was noted even after treatment with iodine for months.—M. B. Gordon.

**Lowered metabolic rates, with special reference to young women.** Smith (P. S.), *South. M. J.* (Birmingham), 1926, 19, 718-723.

In a series of 610 metabolic tests the author finds approximately 45% of the patients with elevated rates and 11% having reduced rates. A plea is made for the promotion of more satisfactory standardization of the various types of metabolism apparatus

and more uniform agreement as to what constitutes an abnormal reading. Excluding the patients with myxedema, cretinism and lowered rates following subtotal thyroidectomy, 31 cases of lowered metabolic rates are reported. Three were males. Ten of the 28 females were of menopausal age and obesity was present in only 25% of the female patients. Special interest is manifested in the incidence of lowered metabolic rates in girls and young women. Of the 31 cases 12 (39%) between the ages of 14 and 25 years are included in the table published. Obesity is usually regarded as a symptom of hypothyroidism, but in these younger patients it was present in only one; five were of normal weight, whereas six (50%) of the twelve patients were definitely underweight. Nervousness, weakness or fatigue—symptoms generally associated with hyperthyroid states—appears seven times (63.5%) as an outstanding complaint in these young females. The records of eight of the twelve patients contain some reference to the thyroid gland; in seven (87.5%) some degree of thyroid fullness was observed. The author concludes that the clinical syndrome of nervousness, unexplained fatigue and thyroid enlargement occurring in young females, many of whom are underweight, cannot be differentiated accurately from hyperthyroidism without an estimation of the patient's metabolic rate. In many such cases with lowered rates thyroid extract appears to have a specific effect.—Author's abstract.

**Angina pectoris as a complication in myxedema and exophthalmic goiter.** Sturgis (C. C.), Boston M. & S. J., 1926, 195, 351-354.

A discussion of four cases.—J. C. D.

**The antagonism of thymus and thyroid. (Zur Frage des antagonistischen Verhaltens von Thymus und Thyreoidea.)** Takao (Tokuriu), Arch. f. d. ges. Physiol. (Berl.), 1926, 23, 192-197.

The loss of liver glycogen in the rat fed thyroid is confirmed. Thymus feeding, either alone, or in different proportions with thyroid, produces no effect. Sodium iodide, in the amounts used, produces no effect. While thyroid feeding produces a marked loss of body-weight, thymus feeding produces a slight rise.—A. T. C.

**The thyrotoxicosis syndrome and the reaction with small iodine doses.** Wahlberg (J.), Acta Med. Scand. (Stockholm), 1926, Suppl. XIV, 148; Abst. Chem. Absts. 20, 3505.

The thyrotoxicosis syndrome is characterized by the common occurrence of a disturbance in thyroid function as is evinced not only from a general clinical investigation but also from a study of the basal metabolism, of the alimentary glucemic reaction and of

the blood pressure. In 20 such patients experiments were carried out to determine the effect of small doses of iodine on the clinical condition as well as on the basal metabolism, pulse rate and body weight, the results showing that these patients betray a characteristic sensitiveness toward the iodine. The primary effect is a general improvement which occurs the more quickly and is the more pronounced, the more intense the thyrotoxicosis syndrome, and which involves the entire syndrome (lowering of the basal metabolism up to 60%, reduction of pulse rate by upward of 40 beats per minute, recession of the exophthalmus, cessation of diarrhea, etc.). By continued treatment this primary effect of the iodine is followed by a secondary exacerbation of the syndrome which is quicker in its onset and more pronounced the more serious the patient's condition was. The condition of a patient may, therefore, actually become much worse under the iodine treatment. At the discontinuance of the treatment the condition also becomes much worse, this being the more pronounced the more serious the thyrotoxicosis of the patient was at the beginning of the treatment. The iodine therapeusis must, therefore, be regarded as offering merely a palliative relief, unless it is resorted to as a preoperative and postoperative treatment, and as a method of therapy should be carefully avoided, especially in the more advanced stages of the disease.

# Endocrinology

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## ON THE MODE OF TRANSPORT OF THYROXIN BY BLOOD

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In a former paper Zavadovsky and Mme. C. M. Perelmuter (1) described a method of detecting the presence of thyroxin in the blood and tissues of hyperthyroidized chickens. Data were also given therein with regard to the distribution of the thyroxin fed to the fowls among the various organs. During the course of the work the facts discovered by us have raised the question of what elements of the blood are responsible for the carrying of the thyroxin.

We have adopted the same method of procedure as described in the previous paper. Chickens were fed 30 grams each of thyroid gland on the eve of the experiment. The chicken was killed the following day and blood was collected from the vessels of the neck. One portion of the blood was diluted with a small quantity of oxalate solution and was centrifuged; the other part was allowed to clot for the purpose of obtaining pure fibrin and fibrinless serum. Various fractions of blood thus obtained were

injected into the bodies of axolotls, of equal body weight as far as possible. These salamanders were then subjected to observation with regard to ability and extent of metamorphosis. In four series of experiments four chickens and one hundred and one axolotls were used. The data for each series are given separately below.

SERIES I—OCTOBER 3RD, 1924

A cock weighing 2570 grams was fed 30 grams of desiccated thyroid gland substance on the eve of the experiment. The blood from this cock was used for eleven axolotls. The serum portion was injected into five, the corpuscle fraction into three, and fibrin

Comparative activity of axolotls' metamorphosis under the influence of various blood fractions.

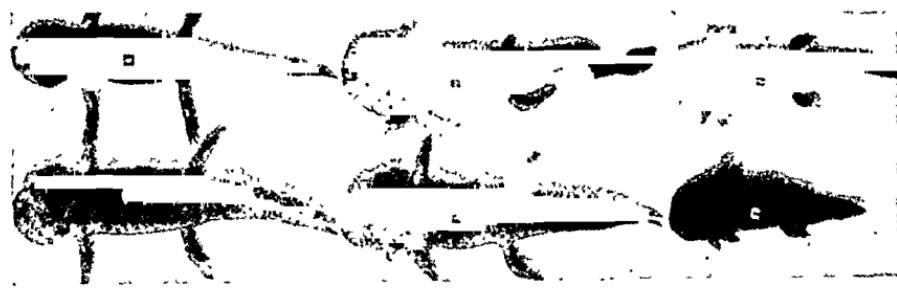


FIG. 1—

- No. 1.—Received 0.3 cc. of serum.
- No. 2.—Received 0.25 cc. of serum.
- No. 3.—Received 1.0 cc. of blood plasma.
- No. 4.—Received 0.25 cc. of blood plasma.
- No. 5.—Received 0.5 cc. of washed erythrocytes.
- No. 6.—Received 0.25 cc. of washed erythrocytes.



FIG. 2—

- No. 1.—Received 0.5 cc. of unwashed erythrocytes.
- No. 2.—Received 0.25 cc. of unwashed erythrocytes.
- No. 3.—Control axolotl of the same family.

previously washed by water into three. Those that died before giving any results were: one injected with fibrin, two with serum and two with corpuscles. The only ones remaining alive and

SHOWING RESULTS OBTAINED BY INJECTION OF BLOOD SERIES II  
October 8th, 1904

Fraction	Dose cc. or grams	No. of avolots	Weight avolots grams	Course of Metamorphosis			Ultimate Result*			Summary		
				12th day	22nd day	35th day	Metamor- phosed	Died before any results	No. result*	Total No.	Metamor- phosis	Partial Metamor- phosis
Serum	0.1	1	4.1	+	+	+			1			
	0.2	1	4.6	++	++	+			1			
	0.1	1	6.7	+++	+++	+	-died metamor- phosis		1			
	0.1	1	7.0	++	++	+			1			
	0.5	1	13.2	++	++	+			1			
	0.2	1	18.0	++	++	+			1			
Plasma	0.1	1	11.6	++	++	+			1			
	0.1	1	3.7	—	—	—			1			
	0.2	1	3.5	—	—	—			1			
	0.4	1	3.5	—	—	—			1			
	0.1	1	5.1	—	—	—			1			
	0.6	1	6.3	—	—	—			1			
	0.6	1	5.0	—	—	—			1			
	0.9	1	7.9	—	—	—			1			
	0.9	1	7.2	—	—	—			1			
Corpuscles unwashed	0.1	1	11.5	+	+	+	-died metamor- phosis		1			
	0.1	1	9.8	+	+	+			1			
	0.2	1	3.7	—	—	—			1			
	0.2	1	3.7	+	+	+			1			
	0.1	1	1.9	+died	+died	—			1			
	0.1	1	5.2	+died	+died	—			1			
Fibrine	0.6	1	7.5	+	+	+			1			
	0.6	1	7.1	+	+	+			1			
	0.6	1	7.0	+	+	+			1			
	0.8	1	9.7	—	—	—			1			
	0.8	1	8.3	+traces	+traces	—			1			
	0.8	1	15.4	+traces	+traces	—			1			
Total	0.6	1	11.1	**	**	**			1			
	31		11.6	**	**	**			1			
*				We mark the degree of metamorphosis reaction conditionally according to the four-ball system, adopted by our laboratory: First phase—shortening of gills and fins. Second phase (2 crosses)—Metamorphosis nearing completion, but with no metamorphosis. Third phase (3 crosses)—Metamorphosis showing no result.			Second phase (2 crosses)—Metamorphosis nearing completion, but with no metamorphosis. Third phase (3 crosses)—Metamorphosis showing no result.			First phase—shortening of gills and fins. Second phase (2 crosses)—Metamorphosis nearing completion, but with no metamorphosis. Third phase (3 crosses)—Metamorphosis showing no result.		
**				First phase—shortening of gills and fins. Second phase (2 crosses)—Metamorphosis nearing completion, but with no metamorphosis. Third phase (3 crosses)—Metamorphosis showing no result.			First phase—shortening of gills and fins. Second phase (2 crosses)—Metamorphosis nearing completion, but with no metamorphosis. Third phase (3 crosses)—Metamorphosis showing no result.			First phase—shortening of gills and fins. Second phase (2 crosses)—Metamorphosis nearing completion, but with no metamorphosis. Third phase (3 crosses)—Metamorphosis showing no result.		

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TABLE II—SERIES III  
SHOWING RESULTS OBTAINED BY INJECTION OF BLOOD FRACTIONS INTO SALAMANDERS OF SERIES III.  
November 10th, 1924.

Fraction	Dose in cc. or gram	No. of axolotls	Weight of axolotl grams	Course of Metamorphosis			Ultimate Results			Summary			
				10th day	19th day	26th day	Metamor- phosed	Died before results	Not com- pleted	No. of axolotls	Metamor- phosis	Partial Metamor- phosis	Non- Metamor- phosed
	0.2	1	2.0	+	+++ near- ly ready	Rendy	1						
	0.25	1	3.2	+	+++ near- ly ready	Ready	1						
	0.3	1	3.5	+	+++ near- ly ready	+	1						
	0.3	1	4.2	+	+++ near- ly ready	Ready	1						
	0.3	1	3.9	+	+++ near- ly ready	Ready	1						
	0.3	1	4.5	+	+++ near- ly ready	Rendy	1						
rum	0.5	1	5.7	+	+++ died	—	1*						
	0.6	1	4.7	+	+++ died	—	1*						
	0.75	1	5.5	+	+++ died	—	1*						
	1.0	1	8.2	+	+++ died	1							
	0.25	1	1.8	+	++ died	+	1						
	0.25	1	3.9	+	++	+	1						
	0.3	1	3.4	+	++	+	1						
	*												
	0.3	1	3.5	+	++ died	+	1						
	0.5	1	4.0	+	++ died	+	1						
	0.6	1	4.5	+	++	+	1						
	0.6	1	5.5	+	++	+	1						
Insm	0.6	1	5.5	+	++	+	1						
	0.75	1	5.5	+	++ died	1	1						
	0.75	1	4.6	+	++ died	—	—						
	1.0	1	10.2	+	++ died	1	1						
					+++ nearly ready								

\*—Metamorphosis partly achieved (nearly ready).

TABLE II—SERIES III—Cont.

Fraction	Dose in cc. or gram	No. of avolts	Weight of avolt grams	Course of Metamorphosis			Ultimate Results			Summary			
				10th day	19th day	26th day	Metamor- phosed	Died before results	Not com- pleted	No. of avolts	Metamor- phosis	Partial Metamor- phosis	Non- Metamor- phosed
Carpules unwashed	0.25	1	4.7		+				1				
	0.25	1	3.5		+				1				
	0.25	1	2.0	Died 3rd day	+	+ meta- morphosis stopped			1	1			
	0.5	1	4.7			+ meta- morphosis stopped			1	1			
	0.5	1	4.5	Died 3rd day	+				1	1			
	0.75	1	5.5		+	+ meta- morphosis stopped			1	1			
	0.75	1	9.1		+	+ meta- morphosis stopped			1	1			
	0.2	1	2.2		—				—	—			
	0.3	1	3.2		—				—	—			
	0.5	1	4.8		—				—	—			
Corpuscles washed	0.5	1	5.9		—				—	—			
	0.05	1	7.9		—				—	—			
Fibrin	0.3	1	4.4	Died on 8th day with no traces of metamor- phosis.					2	0	0	0	2
Total		34							34	10	15	5	4

TABLE III—SERIES IV  
SHOWING RESULTS OBTAINED BY INJECTION OF BLOOD FRACTIONS INTO SALAMANDERS OF SERIES IV.  
March 21st, 1925

Fraction	Dose	No. axolotls	Weight	Course of Metamorphosis			Ultimate Results			Total			
				9th day	20th day	26th day	Metamorphosis	Died no results	Unhanded Metamorphosis	No. axolotls	Metamorphosis	Partial Metamorphosis	
Serum	0.3—0.8	7	—	1 died 5th day	6 ready	6 ready	Ready	1	0	—	7	6	0
Plasma	0.5	1	6.9	+	+ ++ nearly ready	+ ++	Ready	—	—	—	—	—	1
	0.8	1	13.1	+	+ ++	+ ++	—	—	—	—	—	—	—
	1.0	1	9.4	+	+ ++	+ ++	—	—	—	—	—	—	—
	0.5—1.0	4	10.2 Un-known	+ died?	?	?	On 35th day	—	—	—	8	2	6
Pure blood	0.3	1	7.6	+ +	+ +	+ +	—	—	—	1	1	1	1
	0.5	1	7.4	Died 2nd day	Died 2nd day	Died 2nd day	—	—	—	1	1	1	1
	0.5	1	11.7	Died 2nd day	Died 2nd day	Died 2nd day	—	—	—	1	1	1	1
	0.8	1	20.7	Died 2nd day	Died 2nd day	Died 2nd day	—	—	—	1	1	1	1
	1.0	1	12.0	Died 2nd day	Died 2nd day	Died 2nd day	—	—	—	1	1	1	1
	1.0	1	18.7	+ + +	+ + +	+ + +	—	—	—	1	1	1	1
		1	14.0	+ + +	+ + +	+ + +	—	—	—	1	1	1	1
		1	15.2	+ + +	+ + +	+ + +	—	—	—	1	1	1	1
Corpuscles (washed)	1.0	1	13.7	+	+	+	—	—	—	1	—	2	0
	0.75	1	11.7	+	+	+	—	—	—	Traces very dubious	—	—	—
Total		25								25	8	12	5

going through full metamorphosis were two axolotls which received serum. Those injected with fibrin gave no positive results and the remaining ones have shown merely the first traces of metamorphosis. Thus, this first series shows the greater activity of the serum fraction of the blood. The next experiment more precisely carried out left no doubt as to the regularity of this result. See tables I, II, and III.

As may be seen from the results described in table I, series II, all of the eight axolotls which received serum have given evident signs of metamorphosis and four of them entirely completed it; of the ten salamanders which received plasma only one completed metamorphosis, two showed salient symptoms and four gave negative results; of eleven axolotls receiving corpuscles, eight have shown rather doubtful results and three were absolutely negative.

The experiments of series III and IV have given similar results. In this series one other method was used which bears out the deduction of the complete inactivity of the corpuscles. In the first two series we used corpuscles without washing them. In the third series injections of unwashed corpuscles were made, and also injections of corpuscles washed and centrifuged three times in isotonic salt solution. Five axolotls out of the seven receiving the unwashed erythrocytes have shown weak symptoms of metamorphosis. Five animals receiving the washed fraction gave absolutely negative results. The same negative result was obtained with the fraction of unwashed corpuscles in series IV of the experiments. Table IV gives the total summarized results of the experiments performed in these series.

#### CONCLUSIONS

The results obtained allow us to make certain deductions:

(1) The serum appears to play a dominant and exclusive role in the matter of carrying thyroxin. Washed erythrocytes have given negative results, thus leading us to believe that they play no part in the matter of transporting this hormone, at least in quantities capable of being detected by the biological method we are using.

(2) It is interesting to compare this deduction with the newest data of Sbarsky (2), according to which erythrocytes are very important for the transportation of a number of amino

SUMMARY.—TABLE IV

Fraction of Blood	Number of Axolotls	Complete Metamorphosis	Partial Metamorphosis	No Metamorphosis	Died Before Showing Any Results
Serum	30	21 —	7	0	2
Plasma	28	4 —	17 —	4	3
Unwashed corpuscles	21	0	14 —	0	7 —
Washed corpuscles	7	0	Very slight symptoms 0	7 —	0
Fibrin	7	0	0	(Of these, two showed dubious traces) 2 —	5 —
Pure blood	8	0	4 —	0	4
Totals	101 —	25 —	42 —	13 —	21 —

acids adsorbed on the surface of these corpuscles. In so far as we regard thyroxin as a derivative of tryptophane, it might be expected that it would behave like the original amino acid in the blood. Our data make this rather improbable, although they cannot be considered as final, since there is the possibility of the erythrocytes being capable of adsorbing the thyroxin just in those minimal quantities wherein thyroxin is contained normally in the blood of an animal. This possibility is not excluded, because these quantities are beyond the limits of the precision of our method.

(3) The validity of our conclusions is strongly emphasized by results obtained with mixed fractions, such as plasma and unwashed erythrocytes. These fractions give a degree of effect proportional to their content of serum elements.

(4) Our experiments give no direct indication of the ability of fibrin to carry thyroxin, since in five cases out of seven the injection of fibrin gave unexpectedly strong toxic effects in axolotls. On the basis of indirect conjectures, since serum possesses considerably greater activity than plasma, it may be concluded that fibrin is playing here a passive role.

(5) Attention is also attracted by the greater number of deaths among axolotls receiving injections of corpuscles as compared with deaths among those receiving plasma and serum fractions. This phenomenon was shown in all of the series and is not considered as being merely casual.

(6) Finally, the present investigation emphasizes in a still greater degree than in the work of Zavadovsky and Perelmuter, the direct dependence of the intensity of the metamorphosis reaction on the quantity of blood fraction injected, and to a lesser degree on differences in the weights of the salamanders.

The question of the causes of the toxic influences of fibrin and corpuscles, as well as the development of several other phases of this problem, will serve as objects for further investigation.

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# APPLICATION OF THE AXOLOTL METAMORPHOSIS REACTION TO THE QUANTITATIVE ASSAY OF THYROID GLAND HORMONES

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The Biological Laboratory and the Museum of the Sverdlov University have been conducting, since 1921, experiments on the process and conditions of metamorphosis of axolotls under the influence of the thyroid gland. In a number of papers since 1923-24 (1, 2, 3, 4), the method is described of implantation of tissues and organs of animals into the bodies of the axolotls for the purpose of detecting the thyroid gland hormone in those tissues and organs.

In this connection has been discovered not only the possibility of finding thyroxin in the tissues of hyperthyroidized fowls and mammals, but also of making deductions with regard to the quantitative distribution of the thyroxin, depending upon the velocity and degree of axolotl reaction. We base this idea on the natural assumption that the greater the velocity of the metamorphosis, the greater the amount of thyroxin in the tissue implanted into the given axolotl.

Nevertheless, we have found it necessary to make more direct calculations and estimations by our method of biological assay for the purpose of correlating the extent and velocity of the metamorphosis reaction with the quantities of the hormone which we give the axolotls.

We were unable to use conveniently the method of implantation for the solution of this problem, as in all of these cases the amount of thyroxin in the implanted tissue is unknown. We have therefore decided on the method of "concentrations" formerly worked out by us. This method, which is excellent as regards convenience and simplicity, is giving most precise results in all cases in which desiccated thyroid gland substance (pre-

pared for pharmacological purposes by the firms Poehl, Ferrein, and others), is used.

The "concentration" method is essentially as follows: A certain weight of desiccated thyroid gland (Poehl) is mixed with a certain quantity of clean water; axolotls are placed in this thyroidin solution and allowed to remain a certain length of time. We have later learned that this method has also been used by other workers in their work on the metamorphosis of tadpoles. The method is thus based upon absorption of the hormones contained in the solution both through the digestive canals of axolotls swallowing the water and diffusion through the epidermis. There is full opportunity of controlling the precise concentration of the solutions applied. This method of determining the scale of dosages required is considerably more convenient than the former method of feeding axolotls with fresh thyroid gland substance or preparations thereof. Also, our experiments have shown that the entire process takes place within rather precise and regular periods of time, provided the ages of the axolotls and the concentrations applied to them are kept constant. The following two series of experiments illustrate these points.

*Experiment begun December 2nd, 1922.* Twenty-four axolotls hatched between March 18th and 25th, 1921, and weighing from 30 to 50 grams each, were placed in jars of 0.05 per cent thyroidin solution ( $\frac{1}{2}$  gram Poehl's thyroidin per liter of water). Of these, twenty metamorphosed into ambystomae within forty-nine days, and only four individuals died before complete metamorphosis.

*Experiment beginning April 17th, 1923.* Five axolotls hatched in the spring of 1922 were put into a similar 0.05 per cent thyroidin solution. Metamorphosis was completed in fifty-two days. Considering the difficulty of establishing the precise moment of the end of metamorphosis this period of time agrees well with the forty-nine-day period of the former series.

These data have led us to presume considerable consistency and regularity in the time wherein the metamorphosis of axolotls of given weight and age and in given concentrations of thyroidin takes place.

The next series of experiments was planned to give precise data concerning the dependence of metamorphosis in axolotls

TABLE I—SERIES I  
Experiment October 31st, 1924  
AXOLOLTS 30 GR. HATCHED FEB. 21, 1923.  
IN THYROIDIN SOLUTIONS. WATER 2 LITRES. AGE 1 YEAR AND 8 MONTHS.

Concentration, Gms. per 1 cc. water	No. of axolotls	Course of Metamorphosis in Phases and Days						General Results		
		Phase I No. of days	Phase II No. of days	Phase III No. of days	Complete metamor- phosis	Died	Non-met- amorphosed	Number of axolotls	Metamorphosed	After how many days
0.001	I	10	23	27	39			3	3	39
	II	10	23	27	39					
	III	10	23	27	39					
0.0005	I	17	23	27	39			4	4	39
	II	17	23	27	39					
	III	17	23	27	39					
0.0001	I	17	23	27	39			3	3	39
	II	17	23	27	39					
	III	17	23	27	39					
0.00001	I	Merely bulg- ing out of eyes		76	118	Died on 76th day		3	3*	118
	II	Merely bulg- ing out of eyes		76	118					
	III	Merely bulg- ing out of eyes		76	118					
0.000001	I	None meta- morphosed					Merely bulg- ing out of eyes		None metamorphosed, Up to Sept. 1, 1926, merely slight bulging out of eyes.	
	II	None meta- morphosed					Merely bulg- ing out of eyes	6		
0.0000001	I	None meta- morphosed					Merely bulg- ing out of eyes			
	II	None meta- morphosed								

\*We consider that if the first axolotl had not perished in the third phase, it would have metamorphosed at an equal rate.

TABLE II—SERIES II  
Experiment October 31st, 1924  
Axolotls 31 Gr. Hatched March 23, 1923. IN THYROIDIN SOLUTIONS. WATER 2 LITRES. AGE 1 YEAR AND 7 MONTHS.

Concentration, Grams, per 1 cc. of water	No. of axolotl	Course of Metamorphosis						General Results		
		Phase I		Phase II		Phase III		Non- metamor- phosed	Number of axolotls	Complete metamor- phosis
		No. of days	No. of days	No. of days	No. of days	No. of days	No. of days			
0.001	I	10	23	27	39	27	39	Died	3	3*
	II	10	23	27	39	27	39			
	III	10	23	27	39	27	39			
	IV									
	V									
0.0005	I	17	23	27	39	27	39		5	39
	II	17	23	27	39	27	39			
	III	17	23	27	39	27	39			
	IV	17	23	27	39	27	39			
	V	17	23	27	39	27	39			
0.0001	I	17	23	27	39	27	39		5	39
	II	17	23	27	39	27	39			
	III	17	23	27	39	27	39			
	IV	17	23	27	39	27	39			
	V	17	23	27	39	27	39			
0.00001	I	—	34	39	54	54	54		5	5
	II	—	39	54	70	70	70			
	III	—	39	54	70	70	70			
	IV	—	61	76	76	76	76			
	V	—	61	76	118	118	118			
0.000001	I	Bulging out of eyes, slight shortening of gills.	392					1 year 27 days Strong bulging out of eyes, shortening of gills and fins. Slight bulging out of eyes.		54-118
	II	Slight bulging out of eyes.	392							
	III									
	IV									
	V									
0.0000001	I	46	Slight bulging out of eyes.					However none of the five metamor- phosed till Sep- tember 1st, 1926.	2	None metamorphosed.
	II	46	Slight bulging out of eyes.							

\*Assuming that if second axolotl had not died, metamorphosis would have progressed at the same rate.

upon all of these factors. All of the four series of experiments were begun at the end of 1924 and were carried during a period of over one and a half years, until September 21st, 1926. The results of each series are given in separate tables.

In recording the course of the metamorphosis we are using the "four-ball" system adopted in this laboratory. According to this system the first phase of metamorphosis is manifested by a clearly marked bulging of the eyes and the beginning of shortening of gills and fins; the second phase, which represents about a half completed metamorphosis, is marked by the reduction of fins and gills to one-half their original size, and by the eyes acquiring fully the aspect characteristic for *ambystomae*; the third phase shows nearly completed transformation, only the remains of gill rays and fins being still visible, and gill slits not yet closed over; the fourth phase or complete metamorphosis shows full completion of all these processes. As may be seen by comparing the first two tables, showing data obtained from the experiments upon axolotls of different families but of the same age (19 to 20 months), the first three concentrations, from 0.1 to 0.01 per cent gave the same results as to metamorphosis of axolotls, i. e., forty days. Thus, concentrations of more than 0.01 per cent in no way affect the rapidity of metamorphosis of axolotls, except for a somewhat more rapid commencement of phase I in the highest concentrations.

It might be presumed that the velocity of the metamorphosis reaction depends upon some conditions of purely inner character, preventing the completion of metamorphosis in a shorter period. Thus, the period of forty days appears to be the minimum period for full completion of metamorphosis of axolotls of given age and family. No further increase of concentration exceeding 0.1 gram of thyroidin per liter of water affects the velocity of metamorphosis enough to be registered by this biological method.

However, the importance of concentration begins to be seen in going over to lower concentrations of thyroidin. By lowering the concentration tenfold the length of the metamorphosis period is increased by two-thirds. Individual differences are shown under these circumstances. In the maximum concentrations the majority of individuals pass through metamorphosis in the same period of time, forty days; in the lower concentrations different

animals pass through the process in from 54 to 118 days, depending upon the activity of their tissues.

Finally, in using a dose of 0.001 grams per liter in another series, we have seen obvious signs of progressive metamorphosis in two axolotls out of five, but metamorphosis has not been completed even on September 1st, 1926, i. e., after a period of over one and a half years. The other two axolotls of this series have shown only a slight bulging of the eyes. Hence, doses smaller than this are practically ineffective.

These observations have been confirmed by the results of two other series of experiments (see tables III and IV). Considering the results of the first two series we use this time the intermediate dose of 0.03 grams of thyroidin per liter. The axolotls of these two series were younger and lighter in weight than those of the first two series (eight months as compared with twenty months), and this difference was reflected in the greater fineness and sensibility of their reaction. These animals, like those of the other series, have shown full completion of metamorphosis in about forty days, but have also shown a more rapid course of the process after the twenty-fifty day. The dose of 0.03 grams per liter has given practically the same results in animals of the same age, again emphasizing the ineffectiveness of this biological method in distinguishing between different high doses of thyroxin.

It is true, however, that some indication of a more rapid course of metamorphosis in the first concentration, as compared with the second, could be pointed out. Thus, in the third series the animals in concentration 0.0001 (0.1 grams per liter) and those in concentration 0.00003 have shown the first phase of metamorphosis at the same time. However, there is a slight difference in the course of metamorphosis during the first few days in the fourth series under these two concentrations, this difference disappearing towards the end of metamorphosis. Such results lead us to conclude that thyroidin concentration below 0.1 grams per liter may be distinguished from each other by the aid of the method suggested by us, but require a greater number of animals if we are within the limits of the first change from 0.1 grams to 0.03 grams. The next change, from 0.03 to 0.01 grams, is marked by a prolongation of the period required for completion of metamorphosis, although individual differences in reac-

TABLE III—SERIES III  
December 5th, 1924  
AXOLOLTS 44 GR. HATCHED APRIL 11, 1924. THYROIDIN CONCENTRATIONS. WATER 2 LITRES. AGE 8 MONTHS.

Concentration, Grams per 1 cc. water	No. of axolotl	Course of Metamorphosis—No. of Days					Number axolots	Metamorphosed	In what number of days
		Phase I	Phase II	Phase III	Complete metamorphosis	Died			
0.0001	I	10	17	29	35		4	4	25-41
	II	10	17	?	41				
	III	10	?	17	25				
	IV	10	?	17	25				
0.00003	I	10	22	41	45		5	5	32-45
	II	10	22	29	41				
	III	10	22	29	38				
	IV	10	22	29	32				
0.00001	V	10	22	—	—	Died accidentally	5	5	49-110
	I	17	45	?	110				
	II	17	41	45	49				
	III	17	45	49	71				
0.000001	IV	17	45	49	71		5	2	131-434
	V	17	41	45	57				
	I	22	—	—	—				
	II	Bulging eyes	310	428	434				
0.0000001	III	Bulging eyes	—	—	—		4	4	One entered second phase after 360 days; the rest showed no meta- morphosis
	IV	Bulging eyes	—	—	—				
	V	Bulging eyes	?	?	131				
	I	Bulging eyes	360			Died accidentally			
0.00000001	II	Bulging eyes							
	III	Bulging eyes							
	IV	Bulging eyes							
	V	Bulging eyes							

TABLE IV—SERIES IV  
December 5th, 1924.

Experiment completed on September 1st, 1928, with no more metamorphosed.

tion are marked here. This allows us to state that within the limits of concentration between 0.000001 and 0.0001 (the limits of one hundred-fold fluctuation in the quantity of active hormone), the velocity of metamorphosis in axolotls varies parallel with the change in concentration.

It would, however, be a mistake to look for an arithmetical proportionality in the scale. As may be seen from the tables, in changing the concentration from 0.00003 to 0.00001, the length of the period of metamorphosis is only doubled, whereas in changing from 0.0001 to 0.000001 the time of metamorphosis was increased from four to ten times.

The advantage of using smaller animals becomes evident in changing to still lower concentrations, as in group 44 of the third series there are two cases of metamorphosis in 0.000001 concentration between 131 and 434 days. The younger and smaller axolotls not only require lesser quantities of the thyroidin material but show greater sensitivity to the hormone.

#### SUMMARY

1. The velocity of metamorphosis of axolotls under the influence of thyroid gland hormone varies directly, within certain limits, with the concentration of this hormone. This is shown in the application of thyroidin concentration to axolotls of between eight and twenty months in doses of not over 0.1 grams per liter of water and not under 0.001 grams per liter.
2. Larger doses cause no such direct variation because of the inertia of the tissues, and other conditions depending upon the age and individual variations in the animals. The axolotls can not be brought to complete metamorphosis in periods of less than twenty-five to forty days.
3. Smaller doses prove practically ineffective even over a period of action of one and a half years.
4. This biological reaction of metamorphosis in axolotls is quite applicable for the quantitative determination of the thyroxin content in thyroid gland preparations and in animal tissues, provided the above mentioned conditions have been taken into consideration.
5. The most suitable age of axolotls for this purpose is from six to eight months. We have found the best average weight to

be from seven to ten grams. The most suitable dose of thyroidin is about 0.1 grams per liter.

6. It is necessary to consider individual differences in response, some axolotls showing sharp deviations from the average velocity of metamorphosis. Hence, our biological method is valid only statistically and when large numbers of animals are used. Therefore, on the basis of these results and those in previous work, we consider it more suitable to use axolotls in the capacity of indicators to determine the presence of thyroxin.

7. Finally, the important fact should be considered that the threshold concentration of thyroidin for axolotls appears to be about 0.000001. This seems to explain why axolotls do not normally metamorphose into ambystomae, although they do possess rudimentary thyroid glands. Our experiments convince us that for the metamorphosis of axolotls not only the presence of thyroxin is required, but also its presence in certain amounts which are evidently not produced by the normal activity of its own glands. The normal condition of the axolotl is evidently to be regarded not as complete athyroidism but as hypothyroidism.

This work was carried on uninterruptedly over a period of about one and three-fourths years. A considerable amount of the work in connection with observation and attendance on slowly metamorphosed axolotls was done by Mme. C. M. Perelmuter and Mme Lipchina, to whom we wish to offer our thanks.

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transfer the anaphylaxis; furthermore, that the animals can be made anaphylactic passively after thyroidectomy, provided they are treated with the blood of normal sensitized animals.

The thyroidectomized animals may again be sensitized after feeding with thyroid gland preparations. The symptoms of anaphylaxis may appear in animals that are thyroidectomized after sensitization in the usual manner. Houssay and Sordelli did not confirm the above mentioned effects of thyroidectomy in dogs, most probably because the species of the animal is of importance in the results of such experiments.

We have studied the question whether it is possible to increase the sensitiveness of normal guinea pigs by feeding or injection of thyroid extract. We have determined what quantity of antigen suffices, during the reinjection in a thyroid treated animal, to cause shock. The effect of thyroid extract, given shortly before the reinjection, upon the appearance of anaphylactic symptoms has also been determined.

In these experiments it was found that the sensitiveness of guinea pigs was altered by the giving of 1 cc. of thyroid extract every second day. While the reinjection of a 0.05-0.1 cc. of horse-serum was sufficient to cause the death by shock of an animal thus treated, the normal animals died only after the intravenous injection of 0.2 cc. of horse-serum. The thyroid treatment had no specific effect on the anaphylactic drop of temperature and consequently it appears that death was due to greater sensitivity to symptoms of shock. When thyroid extract was given 5 to 10 minutes before the reinjection, 0.05 cc. of horse-serum caused shock, but this hypersensitiveness disappeared within an hour.

Experiments relating to the effect of the parathyroids showed that the sensitiveness of the animals is decreased if parathyroid extract is injected a short time before the reinjection of the serum. In guinea pigs treated for a longer time with parathyroid extract the sensitiveness to shock was not changed.

These effects of parathyroid extract depend also upon the quantity and time of the dose. Guinea pigs weighing from 200 to 250 grams sensitized with horse-serum received 0.25 to 1.0 cc. of parathyroid extract intravenously, 15 to 20 minutes before the reinjection. The antigen dose causing the shock following reinjection was 0.4 to 0.5 cc. of horse-serum, as compared with a

normal antigen dose of 0.2 cc. In a majority of cases a 0.2 cc. dose of horse-serum did not even lead to a drop of temperature. Should the reinjection be given more than 45 minutes after the parathyroid extract its preventive action decreases and after an hour disappears entirely. The experiments were made with a Hungarian parathyroid extract prepared by Collip's method.

These facts seem to prove that the hormones of the parathyroid gland prevent in some way the appearance of anaphylactic symptoms. I am as yet unable to explain the mechanism of this action. It is not impossible that an increase of the blood calcium following parathyroid feeding may play a part in creating the preventive effect.

We found no antagonism in the action of extracts of the anterior lobe of the hypophysis. The appearance of anaphylactic shock symptoms, drop of temperature and death were in no way influenced by an extract of the anterior lobe ("antephysan"), given either once immediately before the reinjection, or over a period of time. Injection of extract of the posterior lobe of the hypophysis (pituglandol, pituitrin, glanduitrin, pituisan) decreased the sensitiveness of guinea pigs; that is to say, the minimal lethal dose of serum was larger than for normal animals. In order to illustrate this effect the results of an experiment will be described.

Guinea pigs were sensitized on October 29th, 1924, with 0.01 cc. of horse-serum. Guinea pigs numbered 17, 18, and 47 received 0.5 cc. of pituglandol intraperitoneally. Reinjections in the jugular vein were made on November 17th.

Animal No. 17 received 0.3 cc. of horse-serum. The temperature fell to below 34° C., but the animal later completely recovered.

Animal No. 18 received 0.35 cc. of horse-serum and showed characteristic symptoms of anaphylactic shock, including the fall of temperature. The animal later recovered.

Animal No. 47 received 0.4 cc. of horse-serum. Symptoms were the same as in animal No. 18 and recovery occurred.

Sensitized control animals untreated with posterior lobe preparations died after receiving 0.2 to 0.25 cc. of horse-serum. Shock symptoms were characteristic.

Hence, after a long treatment with the extract of the posterior lobe the sensitiveness of guinea pigs is really decreased,

transfer the anaphylaxis; furthermore, that the animals can be made anaphylactic passively after thyroidectomy, provided they are treated with the blood of normal sensitized animals.

The thyroidectomized animals may again be sensitized after feeding with thyroid gland preparations. The symptoms of anaphylaxis may appear in animals that are thyroidectomized after sensitization in the usual manner. Houssay and Sordelli did not confirm the above mentioned effects of thyroidectomy in dogs, most probably because the species of the animal is of importance in the results of such experiments.

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In these experiments it was found that the sensitiveness of guinea pigs was altered by the giving of 1 cc. of thyroid extract every second day. While the reinjection of a 0.05-0.1 cc. of horse-serum was sufficient to cause the death by shock of an animal thus treated, the normal animals died only after the intravenous injection of 0.2 cc. of horse-serum. The thyroid treatment had no specific effect on the anaphylactic drop of temperature and consequently it appears that death was due to greater sensitivity to symptoms of shock. When thyroid extract was given 5 to 10 minutes before the reinjection, 0.05 cc. of horse-serum caused shock, but this hypersensitiveness disappeared within an hour.

Experiments relating to the effect of the parathyroids showed that the sensitiveness of the animals is decreased if parathyroid extract is injected a short time before the reinjection of the serum. In guinea pigs treated for a longer time with parathyroid extract the sensitiveness to shock was not changed.

These effects of parathyroid extract depend also upon the quantity and time of the dose. Guinea pigs weighing from 200 to 250 grams sensitized with horse-serum received 0.25 to 1.0 cc. of parathyroid extract intravenously, 15 to 20 minutes before the reinjection. The antigen dose causing the shock following reinjection was 0.4 to 0.5 cc. of horse-serum, as compared with a

normal antigen dose of 0.2 cc. In a majority of cases a 0.2 cc. dose of horse-serum did not even lead to a drop of temperature. Should the reinjection be given more than 45 minutes after the parathyroid extract its preventive action decreases and after an hour disappears entirely. The experiments were made with a Hungarian parathyroid extract prepared by Collip's method.

These facts seem to prove that the hormones of the parathyroid gland prevent in some way the appearance of anaphylactic symptoms. I am as yet unable to explain the mechanism of this action. It is not impossible that an increase of the blood calcium following parathyroid feeding may play a part in creating the preventive effect.

We found no antagonism in the action of extracts of the anterior lobe of the hypophysis. The appearance of anaphylactic shock symptoms, drop of temperature and death were in no way influenced by an extract of the anterior lobe ("antephysan"), given either once immediately before the reinjection, or over a period of time. Injection of extract of the posterior lobe of the hypophysis (pituglandol, pituitrin, glanduitrin, pituisan) decreased the sensitiveness of guinea pigs; that is to say, the minimal lethal dose of serum was larger than for normal animals. In order to illustrate this effect the results of an experiment will be described.

Guinea pigs were sensitized on October 29th, 1924, with 0.01 cc. of horse-serum. Guinea pigs numbered 17, 18, and 47 received 0.5 cc. of pituglandol intraperitoneally. Reinjections in the jugular vein were made on November 17th.

Animal No. 17 received 0.3 cc. of horse-serum. The temperature fell to below 34° C., but the animal later completely recovered.

Animal No. 18 received 0.35 cc. of horse-serum and showed characteristic symptoms of anaphylactic shock, including the fall of temperature. The animal later recovered.

Animal No. 47 received 0.4 cc. of horse-serum. Symptoms were the same as in animal No. 18 and recovery occurred.

Sensitized control animals untreated with posterior lobe preparations died after receiving 0.2 to 0.25 cc. of horse-serum. Shock symptoms were characteristic.

Hence, after a long treatment with the extract of the posterior lobe the sensitiveness of guinea pigs is really decreased,

since the minimum lethal dose is larger than under normal circumstances. A single injection of 0.5 cc. of pituglandol 20 minutes before the reinjection also prevented the appearance of shock. If one succeeds in fixing the optimum time, the pituitary extract given before the reinjection always decreases the sensitiveness of guinea pigs.

Clinical observations permit the conclusion that the failure of function of the female sex glands has a marked effect upon the tone of the autonomic nervous system. Experiments were therefore made to determine the effect of extracts of ovary and corpus luteum on the anaphylactic state in guinea pigs.

Guinea pigs were sensitized in the customary manner. Over a period of sixteen days some were given daily injections of 1 cc. of ovarian extract intraperitoneally, others were given daily 1 cc. of corpus luteum extract. The reinjection was the same in control and experimental animals, *i. e.*, 0.25 cc. of horse-serum, but no difference could be ascertained in either the appearance or result of the shock. Neither did other experiments with extracts of the male sex glands alter the anaphylactic symptoms.

One might conclude from the alleged antagonistic effects between pancreas and thyroid glands that following a reinjection, insulin might reduce the sensitiveness of guinea pigs. Experimentally just the contrary of this happens. The following experiment will illustrate the effect of insulin:

Guinea pig No. 53, weighing 280 grams, showed convulsions 2 hours and 20 minutes after receiving 5 units of insulin (Lilly) intraperitoneally. It recovered 10 minutes later.

A sensitized guinea pig, No. 26, weighing 290 grams, was reinjected with 0.1 cc. of horse-serum during the hypoglycemic period, 2 hours and 40 minutes after receiving 5 units of insulin (Lilly). Death from anaphylactic shock resulted.

A sensitized guinea pig, No. 54, weighing 270 grams, went into hypoglycemic convulsions from 5 units of insulin (Lilly). After complete recovery, 20 minutes after cessation of the convulsions, it was reinjected with 0.1 cc. of horse-serum. The animal died of shock.

A sensitized guinea pig, No. 57, weighing 310 grams, received 6 units of insulin (Lilly). Slight hypoglycemic convulsions were shown after 2 hours and 50 minutes. Three hours after receiving the insulin the animal was given 0.15 cc. of horse-

serum. The temperature fell below 34° C., but the animal recovered.

These experiments demonstrate that both thyroid extract and insulin increase the sensitiveness of sensitized guinea pigs. Adrenalin, parathyroid extract and extract of posterior lobe of the hypophysis all decrease anaphylactic sensitiveness and may prevent the appearance of anaphylactic symptoms. Other gland extracts had no demonstrable effect.

The end results of these briefly described experiments seem to show that the extracts of certain of the endocrine glands have a considerable effect on experimental anaphylaxis. Disorders appearing in the equilibrium of internal secretions, either hypo- or hyperfunction of individual glands, alter the sensitiveness of animals to anaphylactic shock. It would appear that, in anaphylaxis experiments, there is an increase in sympathetic action following sensitization with antigen bodies, whereas the parasympathetics play the greater role in the appearance of anaphylactic shock. Bilateral section of the vagus prevents the appearance of anaphylactic shock, but spontaneous depression or blocking of the cervical sympathetics in no way alter the appearance of anaphylactic symptoms, as our own experiments with Németh have proved. Hence, to characterize the state of the autonomic nervous system as a whole, it may be said that a sensitized animal is in a state of increased sympathetic tonus, while a re-injection is followed by an increase of vagus tonus.

From these considerations it follows that if one wishes to prevent either anaphylactic shock or any other anaphylactic symptoms, or if one should wish to delay the appearance of these symptoms, the sympathetic tonus should be increased or the vagus tonus decreased. Decreasing sympathetic action has no effect upon anaphylactic symptoms and the appearance of these is hastened by increasing vagus tonus.

Baráth, who studied these double effects in this laboratory, concluded that the effect of substances acting upon the autonomic system depends partly on the dose and partly on the state of the active organs.

In anaphylaxis experiments, the same dose of adrenalin causes a fall of blood pressure when injected immediately after the sensitizing with antigen bodies, and causes a rise of blood pressure when injected some time later. The fall in blood pressure

caused by the reinjection is scarcely or not at all influenced by adrenalin given later, as demonstrated by experiments on rabbits.

Clinically, these results seem to be of some practical importance. It would seem that the extracts of the posterior lobe of the hypophysis and of the parathyroids as well as adrenalin might be used at the proper time and in the proper dosage in order to prevent disagreeable anaphylactic symptoms appearing after repeated applications of the widely used therapeutic serum injections. Since insulin increases the shock sensitiveness, repeating the serum injection after a long treatment with insulin should warrant some precaution.

#### SUMMARY

1. Sensitiveness in experimental anaphylaxis is increased by thyroid extract and by insulin; is decreased by parathyroid extract, adrenalin and extract of the posterior lobe of the hypophysis; and is uninfluenced by extracts of the sex glands, corpus luteum and the anterior lobe of the hypophysis.
2. Clinical anaphylactic sensitiveness and idiosyncratic symptoms are increased in hyperthyroidism and exophthalmic goitre, and under insulin and thymus treatment; is decreased by adrenalin, by extracts of the parathyroids and the posterior lobe of the hypophysis, and in myxoedema; and is uninfluenced by extracts of the anterior lobe of the hypophysis.
3. Change in the function of the female sex glands may condition either increased or decreased clinical anaphylactic sensitiveness.

THE EFFECT OF EXTRACTS OF THE POSTERIOR  
LOBE OF THE PITUITARY BODY ON  
THE CIRCULATION

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Since 1895, when Oliver and Schäfer (1) demonstrated a rise of blood-pressure following the intravenous injection of an extract of the pituitary body, much attention has been paid to this organ and the effects of its extracts. The pressor substance was shown by Howell (2) to be obtained solely from the posterior lobe, and he also discovered that second or third injections have a lessened pressor effect.

In 1899, Schäfer and Vincent (3), in a further investigation, showed that in cats anaesthetised initially with ether or chloroform, then with morphia and curare and sometimes atropine, intravenous injections of extracts of posterior lobe of the pituitary body caused, first, a rise, and then in subsequent doses, a fall of blood-pressure. The substance producing the fall was stated to be alcohol-soluble and was not choline.

Later investigations confirmed these results and led to the general statement that intravenous injections of pituitary (posterior lobe) extracts cause, first, a rise, then a fall of blood-pressure.

In 1919, Abel and Kubota (4) claimed to have isolated histamine from the posterior lobe of this gland, and stated that this substance was the depressor substance. Hogben and Schlapp (5) in 1924 found that, after prolonged extraction with alcohol in a Soxhlet apparatus, the depressor effect of subsequent doses of posterior lobe extracts could not be obtained. Hanke and Koessler (6) stated that perfectly fresh pituitary bodies contain no histamine, but that this substance is always present in dried extracts.

The position was at that time that the posterior lobe principle was purely pressor and any depressor effects following the

injection of posterior lobe extracts were due to histamine or to a "histamine-like" substance.

Abel and Geiling and their co-workers (7) claim to have isolated a salt to which they give the name pituitary tartrate, and which, they assert, is in a very highly purified condition. This substance gives, according to these workers, all the actions of pituitary extracts, and they state that second or third or later doses of it produce first, a lessened response, then a fall of blood-pressure. They further claim that the process of purification entirely eliminates any adventitious depressor bodies. Their contention is that the depressor effect of subsequent doses of extracts of the posterior lobe of the pituitary body is an intrinsic property of the pituitary active principle.

While the present paper was being written, a paper by Geiling and Campbell (8) appeared, in which this claim was made, not only for the so-called pituitary tartrate, but also for extracts of posterior lobe extracted with alcohol to remove any contaminating depressor bodies. These workers find that they can still demonstrate the depressor effect of subsequent doses, thus contradicting the conclusions of Hogben and Schlapp who, using the same procedure, failed to obtain a depressor effect.

Geiling and Campbell, however, admit the difficulty of producing a depressor effect, and state that cats anaesthetised with urethane or ether are the most favorable animals, but that even in these animals they cannot always obtain the effect.

Returning to the observations of Schäfer and Vincent, we find, as mentioned above, that in their experiments cats were anaesthetised initially with ether or chloroform and then were put under the influence of morphia and curare and sometimes atropine. Since then, all kinds of experimental conditions have been used, and the diversity of these must account in large part for the mass of conflicting statements made as to the action of the post-pituitary active principle.

It seemed to us then, that a systematic investigation should be undertaken of the effect of extracts of posterior lobe of the pituitary body upon the blood-pressure, firstly under varying conditions of anaesthesia, secondly in different species, thirdly in various doses, and fourthly with various kinds of extracts.

The animals we employed were dogs, cats and rabbits,

anaesthetised with ether or chloralose, and then injected with morphia, morphia and curare, or morphia, curare and atropine.

The extracts were prepared in most cases from fresh ox glands frozen at the slaughter house and brought quickly to the laboratory, where they were either dissected immediately or put into cold storage over night. After dissection they were ground with sand in a mortar with ice cold saline, a drop or two of dilute acetic acid was added to make them just acid to litmus, and the mass brought to the boil and then filtered. This procedure was also carried out with material which had been dried in our laboratories in *vacuo* or dried by manufacturers. The proportion of saline to gland was always 5 cc. of saline to 1 gram. of fresh gland.

After use the extract was sterilized, but we found that 24 hours after the preparation of the extract, chemical changes took place in spite of (or perhaps because of sterilization by boiling), resulting in partial destruction of the pressor principle or, at any rate, the production of sufficient depressor bodies partially to mask the pressor effect. A first injection of this damaged extract might, and frequently did, result in a pure fall of blood-pressure.

The blood-pressure was recorded in the usual way. The vein used for injection was the saphenous in dogs and the external jugular vein in cats and rabbits. The injections were made at room temperature at an appropriate rate. The importance of this will be referred to later.

### *Effects in Dogs*

Whether under ether alone or ether and morphia and atropine (no experiments were performed with curare in dogs), in all cases with all doses of extract of fresh posterior lobe of the pituitary body, pressor effects were at first obtained with each injection. The effect observed was a steady increase in the pressure level after each injection, the new level being maintained for a considerable period—half an hour or an hour in duration. It was noted that later doses had to be increased to produce a pressor effect but, even when subsequent doses were injected at the time when the blood-pressure was near its maximum, no depressor effect could be demonstrated.

*Effects in Cats*

Under chloralose anaesthesia extracts of dried posterior lobe produce successive pressor effects with initial falls of blood-pressure which become more evident with repeated injections. Fresh extracts show no tendency to produce a fall of blood-pressure on subsequent injection, though there is usually a falling off in the pressor response unless increased doses are given.

In cats under ether anaesthesia, successive injections of an extract of fresh pituitary posterior lobe produce effects similar

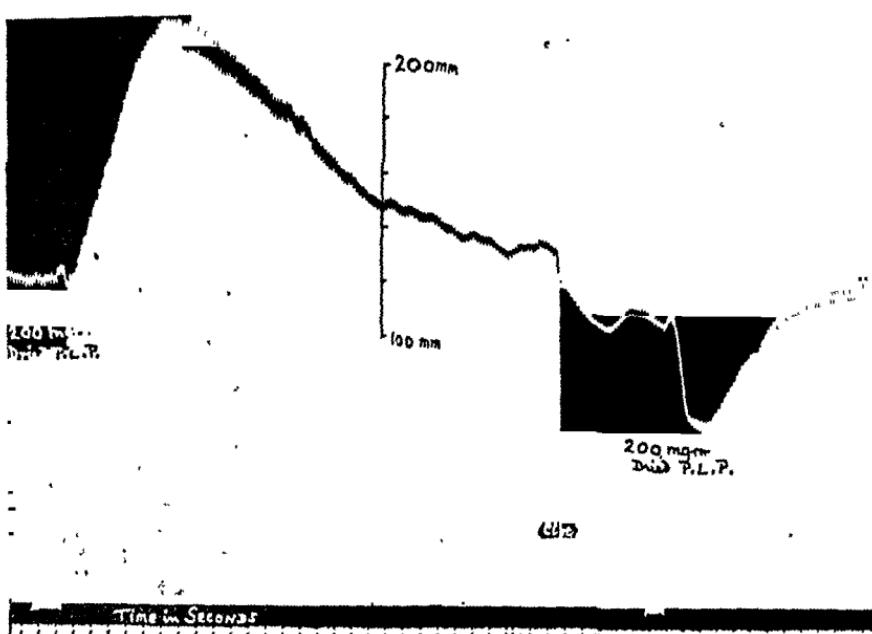


Fig. 3—Cat. Ether: morphia: curare. First injection as shown.

to those recorded in the case of dogs, i. e., a gradual stepping-up of the pressure level which persists a long time, and then a failure to respond to further injections. Extracts of dried material always produce an initial fall of blood-pressure followed by a rise, and this may occur after many injections, but finally the result is purely depressor.

The administration of morphia, either in addition to ether narcosis or following it, makes no appreciable difference to the above results. Atropine, though it abolishes much of the slowing of the heart, does not otherwise alter the response of the circulation.

On administering curare to the morphinised animal, however, a marked difference is observed in the effects of successive injections of the dried posterior lobe extracts. The result of a first injection equivalent to about four-fifths of that used by Schäfer and Vincent, is to produce an enormous rise of blood-pressure, which quickly returns to normal. On repeating the dose a pure depressor effect is obtained. This result is obtained under the same conditions as those with which Schäfer and Vincent worked, and it seems that the combination of morphia and curare alters the circulatory conditions to bring about this effect, which could not in our experiments be demonstrated in any other way. It does not occur with extracts of fresh posterior lobe, but is found only when using dried extracts. Without curare there is always the sustained rise of blood-pressure, which may take an hour to return to its original level.

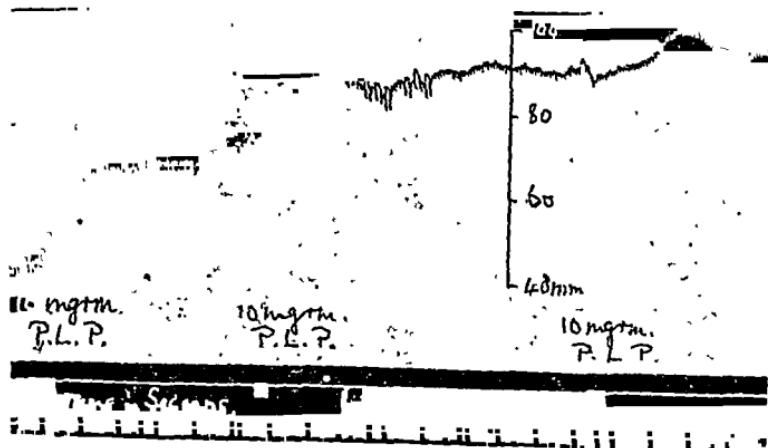


Fig. 4.—Rabbit. Ether: atropine. This animal had had two previous injections of 10 mgm. P.L.P., and just prior to the first injection shown here 3 cc. of 1% atropine sulphate had been administered. Note the successive steps following each injection.

#### *Effects in Rabbits*

Usually the effect of posterior lobe extracts (whether of dried or fresh glands) was to produce a gradual increase of pressure with each injection and then finally no effect. In many cases there is very marked slowing of the heart, but no depressor effect could be demonstrated except under certain conditions to be mentioned later.

*Discussion*

In the above mentioned experiments Geiling and Campbell used an extract of dried posterior lobe which had been soxhled with alcohol for 48 to 72 hours. This procedure rids the substance of depressor bodies, according to Hogben and Schlapp and others. But on a few occasions we have subjected posterior lobe so treated to further soxhleting with chloroform and have been able to demonstrate (in unpublished experiments) that depressor substances may still be extracted.

The extract with which we could not produce a depressor effect was, as described above, obtained from the fresh glands in such circumstances that no depressor substances were formed, or only in infinitesimal amounts. Since we could not demonstrate a depressor effect with this extract, it may be assumed, perhaps, that no depressor bodies were present, for it is asserted that if depressor substances are present, the blood-pressure tracing always shows it by an initial dip occurring before the pressor effect.

Geiling and Campbell obtained their depressor effects ("inversion" as they style it) following second and third injections of posterior lobe extracts under the following conditions: (a) In cats anaesthetised with ether or urethane (they state that dogs are unsuitable for showing the effect); (b) by giving a small dose initially, followed "within a few minutes," by a much larger dose, given before the pressure had returned to normal. They add that rapid injection favors a depressor response.

We had not used urethane and unforeseen circumstances prevented our doing so before the completion of this paper. But using ether or chloralose we have been unable to produce a depressor effect with subsequent injections of extract of posterior lobe freed of depressor bodies. As regards dosage our practice has been to give first a dose of 10 mgm. of posterior lobe and then increased dosage was necessary later to produce a pressor effect (Fig. 1). The time between injections varied from half a minute to quarter of an hour.

The rate of injection is a point of considerable importance which seems to have received little attention. On some occasions we noticed that injection of posterior lobe extracts was

followed by a small fall of blood-pressure. On injecting at the same rate an equal volume of saline at room temperature (the temperature of the extract), an equal fall of blood-pressure was observed. By injecting very slowly no perceptible effect was produced.\*

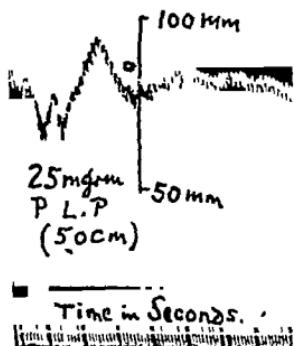


Fig. 5a — Rabbit. Ether.  
This animal had previously  
received 70 mgm. of P.L.P.



Fig. 5b — Two or three  
minutes after 5a in the same  
animal.

Geiling and Campbell's tracings give no record of the rate of injection, and it is possible that too little regard was paid to that point. The depressor effect of saline at room temperature after rapid injection is shown in quite small doses, e. g., 1 cc. It may be observed at the outset of an experiment or more especially after many injections of pituitary extracts.

We think then that Geiling and Campbell's statement that the depressor effect of subsequent doses of pituitary extracts is an intrinsic property of the pituitary active principle, requires further investigation, and that great attention should be paid to the rate of injection.

#### Summary

Extracts of fresh posterior lobe of the pituitary body do not produce a fall of blood-pressure as a result of second or subsequent doses in dogs, cats and rabbits under ether or chloralose anaesthesia with or without morphia, atropine and curare. Under these conditions extracts of dried posterior lobe, on

\* It is noteworthy that, if the fluid is warmed to 37° C. the rate of injection makes no difference to the blood-pressure. The depressor effect of injections made at room temperature is more prone to occur when the injection is near to the heart, as in our experiments with cats and rabbits, but it does occur when the saphenous vein is used.

the other hand, ultimately produce a pure depressor effect owing to contaminating depressor bodies, the contrast between first and second injections being especially marked when morphia and curare are administered to the animal.

The injections should be given at such a rate that equal volumes of saline injected at the same rate will not produce a fall of blood-pressure.

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# CARDAISSLIN: A NEW CARDIAC ACCELERATOR EXTRACTED FROM THE SUPRARENAL GLAND.\*

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## INTRODUCTION

As indicated in a preliminary report (Cameron, H. G.), a new compound has been extracted from the suprarenal glands of cattle.

Tested physiologically, this compound, hereafter called Cardaiissin, has been found to increase the heart rate. It does not affect any other organ than the heart, with the possible exception of the suprarenal glands. It accelerates the rate of the isolated heart of a guinea pig as much as 120 beats for 45 minutes. When injected subcutaneously, it increases the heart rate of various normal mammals for long periods of time.

## PREPARATION OF CARDAISSLIN

A neutral acetone extract of bovine suprarenal glands was made and boiled down to a stiff paste. The fats were removed by means of ether. The residue was then redissolved in alcohol or acetone and purified by fractional precipitation. There were a number of fractions. The first one to be described is Cardaiissin. A more detailed report of the foregoing method will be given at an early date.

By use of the same method on thyroid gland, pancreas, testes, ovary, muscle, kidney, liver, spleen and a lymphatic gland, various extracts were obtained. None of them contained Cardaiissin.

It is well to bear in mind that adrenaline, on the other hand, is isolated from the suprarenal glands by means of an acid solution, usually alcoholic, and then boiled down. Adrenaline is insoluble in neutral alcohol. It stimulates the sympathetic nerve endings, thus increasing the isolated heart's rate for 4 to 7 minutes only; it inhibits movements of the gut and constricts the arteries and arterioles.

\*Read before the Annual Meeting of the Saskatchewan Medical Association, Saskatoon, Sask., September 21, 1926.

## SOME PHYSICAL PROPERTIES OF CARDAISSIN

Cardaissin is a brown gum, soluble in water, and is not destroyed by boiling. It can be dried and weighed, and for the following experiments it was dissolved in physiological saline.

## EXPERIMENTAL

In the experiments which follow, complete protocols were kept in every instance. Tables are appended as examples as well as illustrations. Kymograph tracings were taken where advisable. Working with isolated guinea pigs' hearts, the effect of varying the strength of the dose was studied. The next step was to determine whether successive doses gave the same result. Large quantities were administered to see if there was any difference between the effect of a small and a large dose. Finally

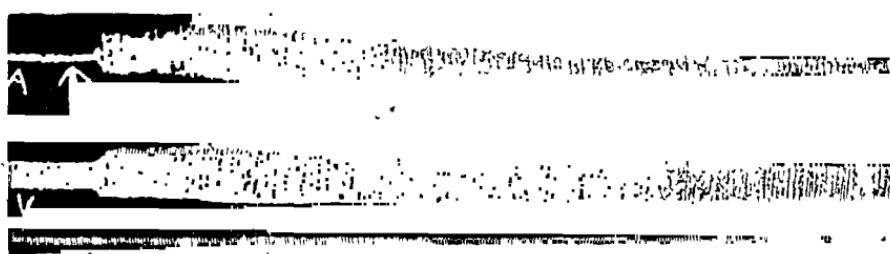


Fig. 1.—The effect of the injection of 1 mgm. of Cardaissin on the rate of the isolated heart of a guinea pig. Kymograph tracing moving from left to right, systole upstroke. One mgm. of Cardaissin was injected into the supply tube as indicated by the arrow. The amplitude of the beat is increased, then the rate is accelerated. A.—Auricle. V.—Ventricle. T.—Time in seconds.

the effect of Cardaissin on the poisoned isolated heart was investigated.

## A. ISOLATED HEART PREPARATIONS

The animal was killed and its heart removed. The aortic stump was connected with the perfusion cannula. A constant, gravity flow of oxygenated Locke's Solution containing 0.1% glucose was maintained at 37 to 38°C. By means of bent pins in the auricle and ventricle attached to two levers, the heart beats were recorded by means of a kymograph. The time was marked off in seconds. Cardaissin was injected into the rubber tubing immediately above the heart cannula.

Fig. 1 is a photograph of a kymographic tracing showing the effect of 1 mgm. of Cardaissin on the isolated heart of animal No. G.P. II, male, 650 grams. The auricles and ventricles

remained equal in rate throughout. Before the injection of Cardaissin, the heart rate was 90 per minute. In 10 seconds after the injection, the amplitude of auricular excursion was three times the normal, and of the ventricular excursion, two times the normal. The rate was 90 per minute. In 30 seconds the auricular amplitude was five times the normal and the ventricular was two and a half times, while the rate remained at 90. In one minute the auricular amplitude was four times and the ventricular was two times the normal, but the rate had increased to 105 per minute. In two minutes the auricular amplitude was two times and the ventricular one and a half times the normal, though the rate was increased to 132. After the kymograph was removed, the rate gradually rose to 170, and the acceleration lasted 30 minutes.

### *1. The Effect of Varying the Dose of Cardaissin.*

The isolated hearts of guinea pigs weighing from 620 to 720 grams were used in order to show the effect of varying the dose.

It was found that 0.5 mgm. of Cardaissin increased the heart rate 60 beats, namely, from 80 to 140 per minute, and the acceleration lasted 15 minutes. On taking another animal, 1 mgm. of Cardaissin increased the heart rate 100 beats, to-wit, from 70 to 170 per minute, and the action lasted 30 minutes. The rate of another isolated heart was increased 120 beats by 1.5 mgm. of Cardaissin, namely, from 60 to 180 per minute, and the increase lasted 46 minutes.

It is quite evident, therefore, that the heart rate acceleration is proportional to the dose of Cardaissin.

### *2. The Effect of Repeated Doses of Cardaissin.*

The same isolated hearts as the foregoing were used for this series of experiments.

The effect of injecting a dose of Cardaissin immediately after a previous one was that, while it stimulated the heart for the same length of time, it did not increase the rate to the same extent.

Thus a study of Table 1 shows that 0.5 mgm. of Cardaissin repeated 10 minutes after a previous and equal dose, lasted 15 minutes but increased the heart rate only 50 beats, namely, 80 to 130 instead of to 140 as formerly. On the other hand, 0.5

mgm. Cardaissin repeated after 53 minutes' rest, increased the heart rate 66 beats. One milligram repeated 30 minutes after a previous and equal dose, increased the heart rate to 140 instead of to 170 as previously.

Therefore it may be said that the rate acceleration decreases with the fatigue of the heart, while the duration of the action remains the same.

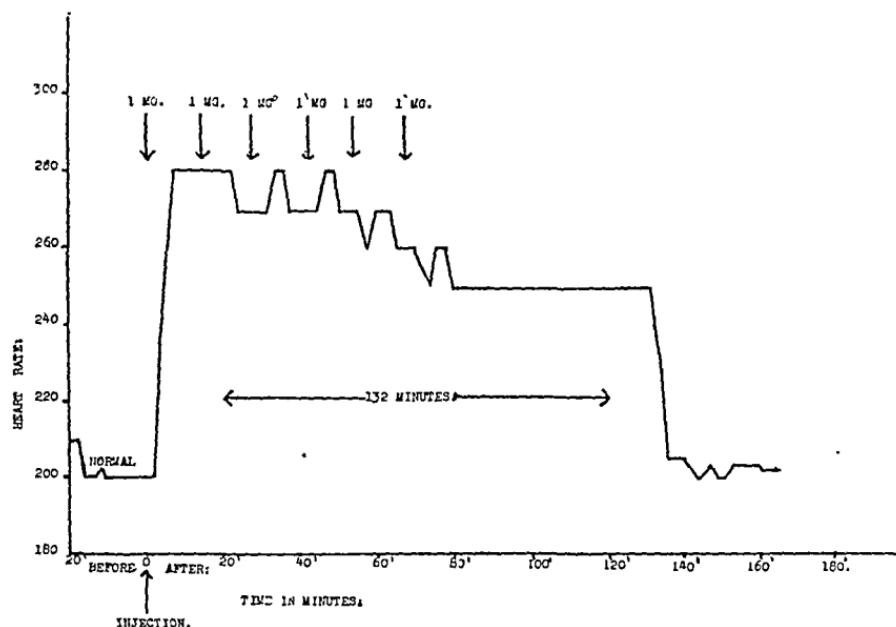


Fig. 2.—The effect of doses of Cardaissin, the injection repeated before recovery to the normal heart rate. One mgm. of Cardaissin was injected into rabbit No. R.7 every 14 minutes, six times, as indicated by the arrows. Ordinates—Heart rate of rabbit. Abscissae—Time in minutes.

TABLE I

Note the marked acceleration with a small dose of Cardaissin. Later there was a decrease in the effect, so that a large dose was required to stimulate the heart. When the auricles and ventricles began to beat at different rates, Cardaissin did not improve the condition to any appreciable extent.

### 3. The Effect of an Overdose of Cardaissin.

The isolated heart of a cat, No. C18, male, 2230 grams, was used for this experiment. Thirty minutes after the death of the animal, the auricles and ventricles were beating at 36 per minute. Twenty mgm. of Cardaissin were injected into the supply tube. The auricles became so rapid in 6 seconds that it was

TABLE I

## THE EFFECT OF 0.5 MGM. CARDAISSIN ON THE ISOLATED MAMMALIAN HEART.

ANIMAL No. G. P. 5, MALE, 680 GRAMS. AUG. 25, 1926.

Time	Aur.	Vent.	Accel.	Temp.	Remarks
P.M.				°C	
1.00	...	...	...	..	
1.15	...	...	...		Guinea pig killed. Perfusion started.
1.20	10	80	0	38	
1.25	40	40	0	..	
1.30	70	70	0	38	
1.35	80	80	0	38	
1.40	80	80	0	37.5	
1.45	70	70	0	38	Strong beat.
1.50	80	80	0	38	
1.55	80	80	0	..	
2.02	...	...	...		
2.03	96	96	16	38	
2.04	110	110	30	..	
2.05	120	120	40	38	
2.06	136	136	56	..	
2.07	140	140	60	..	
2.08	140	140	60	..	
2.09	140	140	60	..	
2.10	140	140	60	38	Strong beat.
2.11	140	140	60	..	
2.12	140	140	60	..	
2.13	136	136	56	38	
2.14	130	130	50	..	Tracing.
2.15	120	120	40		
2.16	110	110	30	38	
2.17	90	90	10	..	
2.18	80	80	0	..	
2.19	80	80	0	..	
2.20	80	80	0	..	
2.21	80	80	0	..	
2.22	84	84	0	38	
2.23	82	82	0	..	
2.24	80	80	0	..	
2.26	80	80	0	..	
2.27	80	80	0	..	
2.28	80	80	0	..	
2.29	...	...	...		1 cc.—0.5 mgm. Cardaissin.
2.30	120	120	40	37.5	
2.32	130	130	50	..	
2.34	130	130	50	..	
2.36	120	120	40	..	
2.38	100	100	20	..	
2.40	98	98	18	..	
2.42	90	90	10	38	
2.44	80	80	0	..	
2.46	78	78	0	..	
2.48	70	70	0	38	
2.50	70	70	0	..	
2.52	66	66	0	38	
2.54	70	70	0	..	
2.56	64	64	0	..	
2.58	60	60	0	..	
3.00	60	60	0	..	
3.02	58	58	0	..	
3.04	60	60	0	37.5	
3.06	60	60	0	..	
3.08	64	64	0	..	
3.10	60	60	0	38	Moderate beat.
3.12	60	60	0	..	
3.14	60	60	0	..	
3.16	60	60	0	38	
3.18	60	60	0	..	
3.20	60	60	0	38	Tracing.
3.22	100	100	40	38	1 cc.—0.5 mgm. Cardaissin.
3.24	120	120	60	..	Strong beat.
3.26					

TABLE I (CONTINUED)

Time	Aur.	Vent.	Accel.	Temp.	Remarks
P.M.				°C	
3.28	126	126	66		
3.30	120	120	60	38	
3.32	100	100	40		
3.34	80	80	20	38	
3.36	70	70	10		
3.38	60	60	0	..	
3.40					No rest.
3.42	104	104	44	38	1 cc.—1 mgm. Cardaissin.
3.44	130	130	50	..	
3.46	140	140	60		
3.48	130	130	50	38	
3.50	100	100	40		
3.52	80	80	20	38	
3.54	70	70	10	..	
3.56	66	66	6		
3.58	60	60	0	38	
4.00	54	54	0		
4.02	54	54	0	38	Normal rate.
4.04	56	56	0		
4.06	54	54	0	38	
4.08	54	54	0	..	
4.10					2 cc.—2 mgm. Cardaissin.
4.12	100	100	46	38	
4.14	120	120	66	..	
4.16	130	130	76		Tracing.
4.18	126	126	72	38	
4.20	124	124	70	..	
4.22	120	120	66	38	
4.24	110	110	56	..	
4.26	100	100	46		
4.28	96	96	42	38	
4.30	84	84	30		
4.32	60	60	6	38	
4.34	52	52	0	..	
4.36	54	54	0	..	
4.38	52	52	0	38	
4.40					1 cc.—5 mgm. Cardaissin.
4.42	124	124	72	..	Tracing.
4.44	126	126	74	38	
4.46	130	130	78		
4.48	130	130	78	38	
4.50	128	128	76		
4.52	124	124	72	38	
4.54	120	120	68	..	
4.56	118	118	66	..	
4.58	116	116	64		
5.00	114	114	62	38	
5.02	112	112	60	..	
5.04	110	110	58		
5.06	110	110	58	38	
5.08	106	106	54	..	
5.10	100	100	48		
5.12	100	100	48	38	
5.14	100	100	48	..	
5.16	100	100	48		
5.18	90	90	38	38	
5.20	84	84	32	..	
5.22	70	70	18		
5.24	60	60	8	38	
5.26	58	58	6	..	
5.28	48	48	0		
5.30	42	42	0	38	
5.32	48	48	0	..	
5.34	46	46	0	..	
5.36	50	50	0		
5.38	50	40	0	38	Weak beat.
5.40	50	30	0	..	
5.42	50	30	0	..	
5.44					1 cc.—20 mgm. Cardaissin.
5.46	62	42	12	38	
5.48	114	60	30	..	

TABLE I (CONTINUED)

Time	Aur.	Vent.	Accel.	Temp.	Remarks
P.M.				°C	
5.50	116	60	30		
5.52	120	80	50	38	
5.54	120	112	82		
7.00	48	44	14	32	
7.02	52	50	20	38	
7.04	54	50	20		
7.06	52	40	10	38	Weak beat.
7.08	50	30	0		
7.10	54	34	0	38	
7.12	48	36	6	38	
7.14	50	30	0		
7.16				.	
7.18	92	48	18	38	1 cc.—20 mgm. Cardaissin.
7.20	96	48	18		
7.22	96	48	18	38	
7.24	94	47	17		
7.26	92	46	16		
7.28	94	47	17	37.5	
7.30	94	47	17	..	
7.32	96	48	18		
7.34	96	48	18	38	
7.36	94	44	14		Weak beat.
7.38	96	48	18		
7.40	92	41	11	38	
7.42	90	41	11		
7.44	90	41	11		
7.46	92	46	16	38	
7.48	90	41	11		
7.50	90	40	10		
7.52	94	41	11	38	
7.54	96	48	18		
7.56	92	41	11		
7.58	90	40	10	38	1 cc.—20 mgm. Cardaissin.
8.00					
8.02	110	50	20	38	
8.04	120	70	40		
8.06	120	80	50	38	
8.08	120	90	60		
8.10	120	90	60	38	
A.M. 9.00	Next morning August 26th.	0	0	20	Beat very weak.

## ABBREVIATIONS

Aur.—Auricular Rate.  
 Vent.—Ventricular Rate.  
 Accel.—Acceleration of Ventricular Rate.  
 Temp.—Temperature of Saline Solution.

impossible to count the beats, which were too small to record on smoked paper. The ventricles contracted and remained in systole for a half minute, then became as rapid as the auricles. The heart did not fibrillate. The beat retained its regular rhythm. The saline was pumped out of the pulmonary artery in small rapid spurts.

A large dose of Cardaissin accelerates the heart rate indefinitely, but does not cause it to fibrillate.

It may be noted that a large dose of adrenaline or the repetition of one causes the heart to fibrillate (Sharpey-Schafer, 1924).

*4. The Effect of Cardaissin on the Arrested Heart.**(a) Due to Lack of Physiological Saline.*

The isolated heart of animal No. G.P. 16, male, 660 grams, was set up and the perfusion fluid cut off for an hour and a half, so that, while the auricles were beating weakly, 80 per minute, the ventricles were stopped. On injecting 2 mgm. of Cardaissin into the heart through a side tube, the rates of both auricle and ventricle increased to 104 per minute. This acceleration lasted for 14 minutes. (Normally 0.5 mgm. increased the rate to 140, lasting 15 minutes.) On turning on the Locke's solution, the heart was again accelerated to 104 beats per minute and this effect lasted 34 minutes.

*(b) Due to a Lack of Salts in the Perfusion Fluid.*

The isolated heart of animal No. G.P. 4, male, 610 grams, was attached to the perfusion apparatus. Distilled water kept at 38°C. was used as perfusion fluid. In twenty minutes after attaching the heart to the cannula, the auricle was beating at 10 per minute and the ventricle had stopped. On injecting 1 mgm. of Cardaissin into the distilled water supply tube, both the auricular and ventricular rates were increased to 80 beats per minute and the effect lasted 10 minutes. Then the ventricle stopped. On starting warm physiological saline through the heart, it was again increased in rate to 110 per minute and this effect lasted 14 minutes. It was then beating at a rate of 70, which it maintained for some time.

Apparently Cardaissin can stimulate a heart, which has been stopped, by perfusing it with distilled water, but the acceleration is of short duration, until physiological saline is supplied.

*(c) Due to a Lack of Oxygen in the Perfusion Fluid.*

Animal No. G.P. 23, male, 650 grams, was used for this experiment. The guinea pig was killed at 12:30 p. m. The heart was attached to the cannula at 12:50, and the perfusion started. The heart beat at 72 per minute. The oxygen was not turned on. The temperature of the Locke's solution was maintained at 38°C. By 1:24 the auricles beat at 30 per minute, while the ventricles were stopped in diastole. At 1:26, 1 mgm. of Cardaissin was injected into the supply tube. The

ventricle started to beat immediately, then auricles and ventricles increased in rate steadily until they were both at 160 per minute. Suddenly, 8 minutes after the injection, they slowed down, so that the auricles were 88 and the ventricle 44. Then the oxygen was turned on and in 30 seconds the heart rate was 100 and in 4 minutes 150. This second acceleration lasted 15 minutes, when the heart rate returned to 74 per minute, which it maintained for over an hour.

Cardaissin, while stimulating the heart in the absence of oxygen, is not a substitute for the latter.

(d) *Due to Lack of Heat.*

The temperature of the oxygenated Locke's solution, perfusing the isolated heart of guinea pig No. G.P. 3, male, 630 grams, was allowed to become 20°C. The ventricles stopped and the auricles beat at 20 per minute. On injecting 2 mgm. of Cardaissin into the supply tube, the auricles and ventricles beat at 100 per minute. Twenty mgm. were then injected and the preparation left for the night. The next morning the auricles were beating weakly at 30 and the ventricles 4 per minute.

As a check, another isolated heart from animal No. G.P. 20, male, 640 grams, was set up and the oxygenated fluid kept at 37°C. It beat for two and a half hours.

Cardaissin counteracts the slowing produced by cooling the heart.

5. *The Effect of Cardaissin on the Poisoned Heart.*

(a) *Chloroform.*

The isolated heart of guinea pig No. G.P. 12, male, 600 grams, was used for this experiment. It was beating at 80 per minute. Both its auricles and ventricles were stopped by administering to it chloroform water equivalent to 6 mgm. Sixteen milligrams of Cardaissin were injected into the supply tube. The auricles, 10 minutes later, beat at 62 and the ventricles 30 per minute. At the end of an hour they were both beating at 14 per minute.

Next the effect of injecting the Cardaissin and then the chloroform was studied. Animal No. G.P. 14, male, 620 grams, was killed at 3:10 p. m., and at 3:20 its heart was attached to the perfusion apparatus. The heart rate became constant at 60

per minute. At 3:50, 15 mgm. were injected into the supply tube. The beat was so rapid and small that it could not be counted. On injecting 2 cc. chloroform water containing 1.76 mgm., the beat decreased to 160 per minute. The strength of the beat increased with the slowing. Sixteen minutes later, 1 cc. chloroform water containing 4.4 mgm. in solution was administered. The heart rate slowed to 60 beats for 4 minutes, then increased to 140; finally an hour later it had decreased to 40 per minute.

While 16 mgm. of Cardaissin failed to counteract 6 mgm. of chloroform, a total of 6.16 mgm. chloroform did not completely abolish the effect produced by 15 mgm. Cardaissin.

Evidently Cardaissin inhibits the poisonous action of chloroform on the heart muscle and chloroform counteracts an overdose of Cardaissin.

#### (b) *Pilocarpine.*

Cat No. C 19, female, 2240 grams, was used for this experiment. At 3:00 p. m. its heart was attached to the perfusion apparatus. The heart remained at 50 per minute for over an hour. At 4:46, 2 cc. physiological saline solution containing 1.3 mgm. pilocarpine nitrate were injected into the supply tube. In one minute the auricle was beating weakly at 10 per minute, while the ventricle was paralyzed. Six minutes after the injection, the auricle was two per minute, then ceased beating two minutes later. Nine minutes after the pilocarpine, 2 mgm. of Cardaissin were injected into the supply tube. The auricles and ventricles immediately started to beat at 20 per minute and then 40. Finally, thirty minutes after this last injection of Cardaissin, they beat at 80 per minute.

Cardaissin revives and accelerates the rate of a heart which has been poisoned with pilocarpine.

#### (c) *Strychnine.*

The heart from guinea pig No. G.P. 8, male, 770 grams, was used. The heart beat was 70 per minute. The ventricle was stopped by injecting 11 mgm. strychnine sulphate into the supply tube. Then, two minutes later, 1 mgm. Cardaissin was administered. It revived the heart, so that in 6 minutes both

auricle and ventricle were beating quite forcibly at 80 per minute.

(d) *Morphine.*

The isolated heart of guinea pig No. G.P. 9, male, 600 grams, was used to test the effect of Cardaissin and morphine. Two hours after the animal was killed, the heart rate was 42 per minute. As is shown in Figure 3, it was poisoned with 65 mgm. of morphine sulphate stopping both auricle and ventricle. Then 2 mgm. of Cardaissin were injected into the supply tube and the heart was revived so that in 6 minutes its rate was 70.

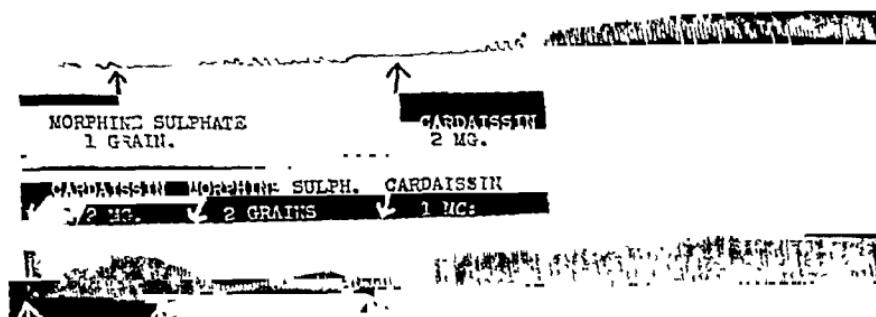


Fig. 3.—The effect of Cardaissin on an isolated heart poisoned with Morphine. Kymograph tracing moving from left to right, systole upstroke. Ventricle only.

Upper Curve—one grain Morphine Sulphate was injected at first arrow. The Morphine stops the heart beat, while Cardaissin revives and accelerates it. Lower Curve—same heart 30 minutes later. One-half mgm. of Cardaissin was injected at the first arrow, 2 grains of Morphine Sulphate at the second arrow and 1 mgm. of Cardaissin at the third arrow. Morphine slows but does not stop the heart, which is under the influence of Cardaissin.

Thirty minutes later, when the rate had increased to 40 per minute, 0.5 mgm. of Cardaissin was injected into the supply tube. Then 130 mgm. of morphine sulphate was administered. As is demonstrated in Fig. 2, this large dose failed to stop either the auricle or ventricle, although the poison slowed them. One mgm. of Cardaissin accelerated the rate to 90 per minute when injected into the supply tube 1 minute after the morphine.

In general, Cardaissin counteracts the cardiac depressant action of the poisons, chloroform, morphine, strychnine and pilocarpine. If Cardaissin is given before the poison, it requires less to counteract the effect than if the poison is given first.

(e) *Adrenaline.*

The heart of guinea pig No. G.P. 11 was used to study the effect of the contiguous injection of Cardaissin and adrenaline.

One milligram of Cardaissin was injected into the supply tube at 1:50 p. m., and a tracing taken. By 2:38 the heart was back to normal, namely, 84. At 2:40, 1 mgm. of adrenaline hydrochloride was injected. The auricles and ventricles went into fibrillation, which lasted one minute. Then the heart started again. Its contractions improved and its rate increased to 90 per minute. This acceleration due to adrenaline lasted 7 minutes. Twenty minutes later, when the heart rate was 54 per minute, 1 mgm. of Cardaissin was injected into the supply tube. As is shown in Fig. 4, the auricles fibrillated for 20 seconds. Then both auricles and ventricles commenced to contract forcibly and in one minute's time beat at the rate of 63 per minute. In three minutes the rate was 75 per minute. The beats were

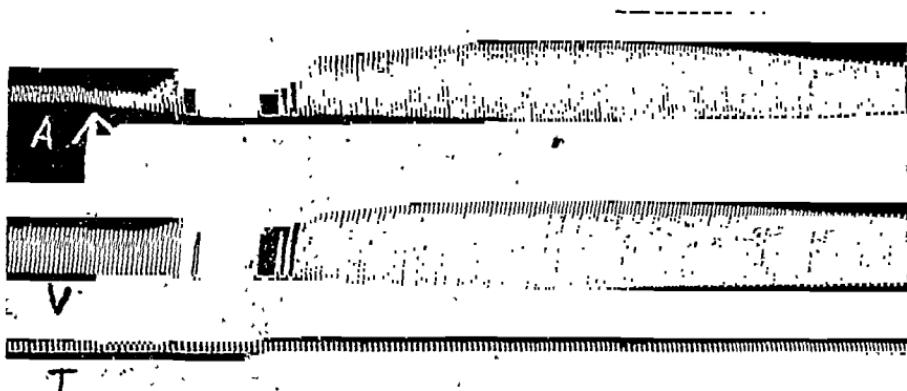


Fig. 4.—The effect of Cardaissin administered to an isolated heart recovering from Adrenaline injection. Kymograph tracing moving from left to right, systole upstroke. One mgm. Cardaissin was injected at arrow. Note auricular fibrillation. A.—Auricle. V.—Ventricle. T.—Time in seconds.

alternately large and small. It bore a striking similarity to the clinical condition, "pulsus alternans." After the removal of the kymograph, the rate increased to 94 per minute and the acceleration lasted 30 minutes. There was no difference between the auricular and ventricular rates, except when the auricles were fibrillating, then the ventricle beat slowly and strongly.

#### B. THE EFFECT OF CARDAISSIN ON OTHER ORGANS

The effect of Cardaissin on other organs and tissues of the animal body was next examined. Whether or not it constricted the arteries was determined by a study of the action of Car-

daissin on the isolated aorta. Then its effect on isolated strips of smooth muscle, such as the gut and uterus, was studied. Finally the results of treating striated muscle, nerves, kidneys and glands with Cardaissin were investigated.

### 1. *The Effect of Cardaissin on the Arteries.*

A spiral band of cat's aorta was attached to a recording lever and immersed in aerated physiological saline, kept at 38°C. On adding 2 mgm. of Cardaissin to the containing beaker, the band did not contract; whereas, on the addition of 1 mgm. of adrenaline, it did. The strengths of the solutions in the bath were, respectively, Cardaissin 1 in 75,000, and adrenaline 1 in 150,000.

A ring of cat's aorta was treated in the same way with the same negative result for Cardaissin and a positive one for adrenaline.

On injecting 1 mgm. of Cardaissin into the ear of a rabbit, the blood vessels of that ear were not constricted.

Cardaissin does not constrict the blood vessels, while adrenaline does.

### 2. *The Effect of Cardaissin on Other Smooth Muscle.*

A piece of cat's ileum was attached to a lever just as was the aorta and its contractions recorded. On adding 1 mgm. of Cardaissin there was no change in the gut movements. On the other hand, adrenaline immediately caused the loop to relax and all movements to cease.

The smooth muscle of the eye was not affected when Cardaissin was injected into the blood stream, nor when it was dropped into the eye itself; it had no effect on the enucleated organ.

Cardaissin, further, had no effect on the isolated uterus of a non-pregnant cat. It had no oxytocic effect on a pregnant rabbit near term. When injected into the gall bladder there were no contractions.

Cardaissin has no effect on smooth muscle.

### 3. *The Effect of Cardaissin on Striated Muscle.*

Cardaissin did not affect the voluntary muscles of the normal animal. It did not vary the contractions produced by electrical stimulation of an isolated nerve-muscle preparation.

#### 4. *The Effect of Cardaissin on the Nerves.*

Cardaissin did not irritate the cut end of a nerve nor affect the nerve arc, when injected into the femoral nerve sheath.

#### 5. *The Effect of Cardaissin on the Kidneys.*

The urinary secretion of cat No. C 21 was the same before and after the injection of 1 mgm. of Cardaissin as was shown by the number of drops falling from cannulas in the ureters. The urine remained normal as regards sugar, albumen and blood. At autopsy the kidneys were found to be normal.

#### 6. *The Effect of Cardaissin on the Glands of Digestion.*

Cardaissin did not increase the salivary secretion of the normal mammal.

### C. THE EFFECT OF CARDAISSIN ON THE HEART RATE OF A NORMAL MAMMAL

A healthy female gray rabbit, No. R. 7, 2560 grams. was selected for this series of experiments. The first hypodermic dose of 0.5 mgm. of Cardaissin accelerated the heart rate 90 beats and the effect lasted 54 minutes; whereas, after this first injection, that same amount increased the rate by 50 beats and acted for only 11 minutes. The reason for this early augmentation will be discussed later. The only difference in the effect of hypodermic and intravenous injections of Cardaissin was that by the former method it required 4 minutes before it began to take effect, whereas by the latter it was almost instantaneous in its action. The ears always became hot soon after the injection. The respirations increased with the heart rate. The urine remained normal. The rabbit was still in good health three weeks after the injections.

The effect of increasing the amount of Cardaissin injected was studied. Then the result of repeating the dose was investigated. Finally in the rabbit conditions arising from the injection of a large or over-dose were observed.

#### 1. *The Effect of Graded Doses of Cardaissin on the Heart Rate.*

The rabbit was trained to remain quiet while these observations were being made. The heart rate was counted by means of the stethoscope, which was held constantly over the apex area

throughout the experiment. A great deal of practice was required before the very fast rates could be determined. The counting was done in tens for half-minute periods, which were repeated every two minutes.

As can be seen in Fig. 5, if a period of 4 minutes is allowed for absorption of the Cardaissin, then:

0.5 mgm. Cardaissin accelerated heart rate 50 beats, the effect lasting 11 minutes.

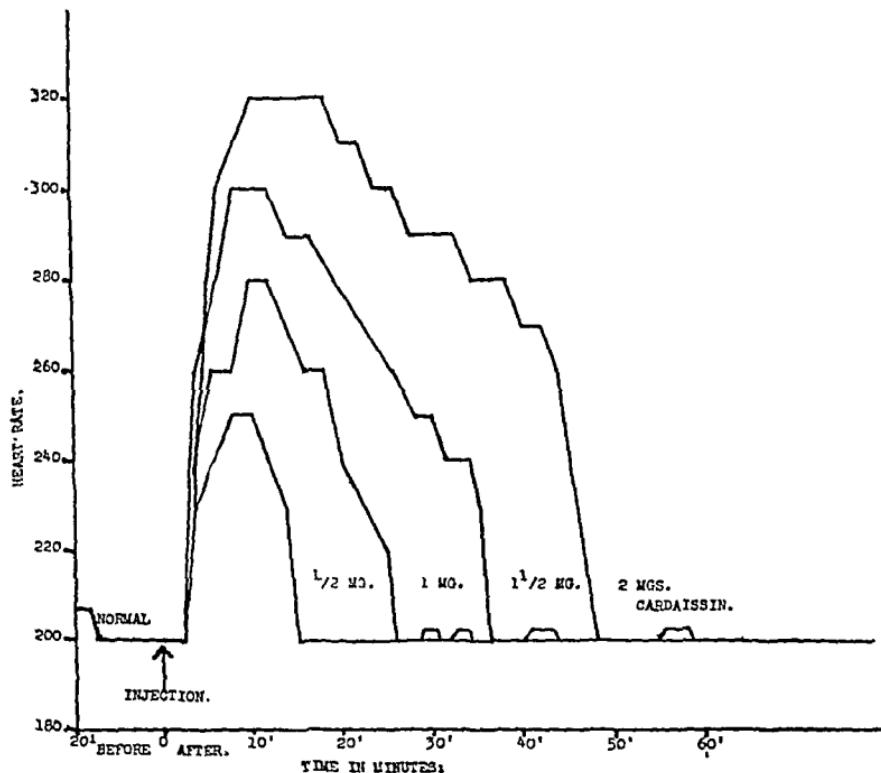


Fig. 5.—The effect of graded doses of Cardaissin on the heart rate of a normal mammal. Rabbit No. R.7, 2560 grams. Doses of Cardaissin, 0.5 mgm., 1 mgm., 1.5 mgm., 2 mgm., were injected subcutaneously into the rabbit at the times indicated by the arrows. Ordinates—Heart rate of rabbit. Abscissae—Time in minutes, zero being the point of injection.

1.0 mgm. Cardaissin accelerated heart rate 80 beats, the effect lasting 22 minutes.

1.5 mgm. Cardaissin accelerated heart rate 100 beats, the effect lasting 33 minutes.

2.0 mgm. Cardaissin accelerated heart rate 120 beats, the effect lasting 44 minutes.

As the dose of Cardaissin is increased, so is the heart rate and the duration of the effect.

*2. The Effect of Repeated Doses of Cardaissin.*

*(a) After the Heart Rate Had Returned to Normal.*

Again allowing 4 minutes for absorption, 0.5 mgm. Cardaissin was injected three times, after the heart had returned to its normal rate for some 20 minutes, and every time the acceleration lasted 11 minutes. But the acceleration decreased as the heart became more fatigued. Thus:

First injection of 0.5 mgm. of Cardaissin accelerated the heart rate 50 beats.

Second injection of 0.5 mgm. of Cardaissin accelerated the heart rate 40 beats.

Third injection of 0.5 mgm. of Cardaissin accelerated the heart rate 40 beats.

Fourth injection of 0.5 mgm. of Cardaissin accelerated the heart rate 30 beats.

The effect of 1 mgm. of Cardaissin repeated in 10 minutes and after three hours was determined. The duration was 22 minutes for all four injections. The results are herewith summarized:

First injection of 1 mgm. Cardaissin accelerated the heart rate 80 beats. Rest of 10 minutes.

Second injection of 1 mgm. Cardaissin accelerated the heart rate 60 beats. Rest of 3 hours.

Third injection of 1 mgm. Cardaissin accelerated the heart rate 80 beats. Rest 12 minutes.

Fourth injection of 1 mgm. Cardaissin accelerated the heart rate 60 beats.

The duration of the effect of 1.5 mgm. of Cardaissin was 33 minutes for all four injections, but the acceleration varied in the following manner:

First injection of 1.5 mgm. Cardaissin accelerated the heart rate 100 beats. Rest 25 minutes.

Second injection of 1.5 mgm. Cardaissin accelerated the heart rate 80 beats. Rest 3 hours, 10 minutes.

Third injection of 1.5 mgm. Cardaissin accelerated the heart rate 100 beats. Rest 10 minutes.

Fourth injection of 1.5 mgm. Cardaissin accelerated the heart rate 60 beats.

The duration of the action of 2 mgm. Cardaissin was 44 minutes for both injections, and the acceleration of the rates was as follows:

First injection of 2 mgm. Cardaissin accelerated the heart rate 120 beats. Rest 16 minutes.

Second injection of 2 mgm. Cardaissin accelerated the heart rate 80 beats.

Cardaissin had no effect when administered "per os."

From the foregoing it can readily be seen that the acceleration of the heart, after the injection of Cardaissin, varied with the fatigue of the heart muscle. But the duration of its action remained the same for all equal doses.

## 2. (b) *Before the Heart Rate Had Returned to Normal.*

It is important from the clinical point of view to find out if Cardaissin can keep the heart rate moderately accelerated over a long period of time, hence the following experiments were performed. Cardaissin was injected in small doses at short intervals, before the rate had returned to the normal.

One-half milligram Cardaissin was injected into rabbit No. R-7 every 8 minutes until 4.5 mgm. had been administered. The heart rate rose to 250 per minute, then dropped to 240. After each injection it was increased to 250. It was interesting to find that instead of returning to its normal rate 11 minutes after the last injection, it continued accelerated at 240 per minute until 90 minutes after the first injection. Finally it returned to its normal rate 99 minutes after the Cardaissin first started to act. The data are summarized in Table II:

On the afternoon of the foregoing experiment (September 1st), 6 mgm. was injected into the rabbit No. R-7. It was administered in 1 mgm. doses, repeated every 14 minutes. As is shown in Fig. 8, the heart rate increased from 200 to 280 beats per minute. The rate continued to fluctuate 10 beats, while the Cardaissin was being injected; then it remained accelerated at 250 beats per minute, for one hour after the last injection. The heart rate was accelerated 80 beats and less, for 132 minutes after the fractional injection of 6 mgm. It is thus shown that large amounts may be administered fractionally, without in-

TABLE II  
REPEATED DOSES OF CARDIASSIN BEFORE RECOVERY TO NORMAL HEART RATE  
FOUR AND FIVE-TENTHS MGCS. CARDIASSIN INJECTED HYPODERMICALLY INTO RABBIT NO. R7. SEPTEMBER 1ST, 1926.  
FIVE-TENTHS MG. DOSE REPEATED EVERY 8 MINUTES.

Time	Rate	Accel.	Remarks		Time	Rate	Accel.	Remarks
			A.M.					
9.30	210	0			10.48	240	40	
9.32	210	0			10.50	250	50	Ears hot.
9.34	200	0			10.52	250	50	
9.36	200	0			10.54	240	40	1 cc.—0.5 mgm. Cardiaassin.
9.38	200	0			10.56	240	40	Ears hot.
9.40	200	0	Ears cold.		10.58	250	50	
9.42	200	0			11.00	250	50	
9.44	200	0			11.02	240	40	
9.46	200	0			11.04	240	40	Bvs. in ears dilated.
9.48	200	0			11.06	240	40	
9.50	200	0	1 cc.—0.5 mgm. Cardiaassin.		11.08	240	40	
9.52	200	0			11.10	240	40	
9.54	230	40			11.12	240	40	
9.56	240	40			11.14	240	40	
9.58	250	50	1 cc.—0.5 mgm. Cardiaassin.		11.16	240	40	
10.00	250	50			11.18	240	40	
10.02	250	50			11.20	240	40	
10.04	240	40	Ears hot.		11.22	234	34	Ears cool.
10.06	240	40	1 cc.—0.5 mgm. Cardiaassin.		11.24	230	30	
10.08	240	40			11.26	224	24	
10.10	250	50	Ears hot.		11.28	226	26	
10.12	250	50			11.30	222	22	
10.14	240	40	1 cc.—0.5 mgm. Cardiaassin.		11.32	210	10	
10.16	240	40			11.33	200	0	
10.18	250	50	Ears hot.		11.34	202	0	Ears cold.
10.20	250	50			11.36	202	0	
10.22	240	40	1 cc.—0.5 mgm. Cardiaassin.		11.38	202	0	
10.24	240	40			11.40	200	0	
10.26	250	50	Ears hot.		11.42	200	0	
10.28	250	50			11.44	200	0	
10.30	240	40	1 cc.—0.5 mgm. Cardiaassin.		11.46	200	0	
10.32	240	40			11.48	200	0	
10.34	250	50	Ears hot.		11.50	200	0	
10.36	250	50			11.52	200	0	
10.38	240	40	1 cc.—0.5 mgm. Cardiaassin.		11.54	200	0	
10.40	240	40			11.56	200	0	
10.42	250	50	Ears hot.		11.58	200	0	
10.44	250	50			12.00	200	0	
10.46	240	40	1 cc.—0.5 mgm. Cardiaassin.					

## ABBREVIATIONS

Rate—Heart Rate.

Accel.—Acceleration of the Heart Rate.

The readings of the heart rate were made with the stethoscope every two minutes, except when the rate began to decrease, then they were made every minute.

curing the dangers of an overdose. The duration of the effect depends on the total amount of Cardaissin injected, thus:

- 0.5 mgm. Cardaissin acts for 11 minutes.
- 4.5 mgm. Cardaissin acts for 99 minutes.
- 1.0 mgm. Cardaissin acts for 22 minutes.
- 6.0 mgm. Cardaissin acts for 132 minutes.

### 3. *The Effect of a Large Dose of Cardaissin on a Normal Mammal.*

Ten milligrams of Cardaissin was injected into a healthy white rabbit, No. R-22, male, 2400 grams, subcutaneously. The animal became restless and excited and its respiration rapidly increased to over 300 per minute. The heart rate quickly mounted from 180 per minute to 360, then to 380. At this point the valves made no sound of closing. The ears became cold and pale. Neither the femoral nor the carotid arteries could be palpated. Suddenly the valves would make the sound of closing and the rabbit would spring to life, only to fall back again into coma as the circulation failed. Twenty-minutes after the injection the heart rate was over 400 beats per minute. One hour after the injection the heart suddenly stopped beating.

At autopsy, the lungs were seen to be markedly congested, the auricles dilated and the ventricles in systole. Examination of microscopic slides of the lungs, kidneys and liver showed them to be congested, but exhibiting no other pathological lesion. The heart muscle was normal in appearance. The most noticeable fact was that in both suprarenal glands the medulla was markedly vacuolated.

A large dose of Cardaissin accelerates the heart rate to such an extent that it finally causes the death of the animal. The heart failure is doubtless due to a mechanical breakdown, owing to the valves failing to close.

#### D. THE EFFECT OF CARDAISSIN ON VARIOUS NORMAL ANIMALS

The effect of Cardaissin in the guinea pig was the same as in the rabbit, except that an equal dose had a greater effect. Thus, after the preliminary effect, 1 mgm. accelerated the guinea pig's heart 320 beats and lasted for 88 minutes; whereas an equal dose had increased the rabbit's heart 80 beats and acted for 22 minutes. The rabbit weighed 2560 grams and the guinea pig 640.

The effect of 1 mgm. of Cardaissin injected into a male cat weighing 2360 grams was the same as in the rabbit.

THE EFFECTS OF CARDAISSIN ON THE HEART RATE OF A  
NORMAL MAN

A man in good health, age 31 years, weighing 90 kilos., was used for this series of experiments. The heart rate was counted by means of the stethoscope, which was held over the apex area, while the individual was seated.

The preliminary effect was provided for by the subcutaneous injection of 0.5 mgm. of Cardaissin. This amount accelerated the heart 10 beats and lasted 8 minutes. The next day 1 mgm. was injected hypodermically, and the series continued from them on. Allowing 4 minutes for absorption, the following results were obtained:

1 mgm. Cardaissin accelerated the heart rate 12 beats and lasted 9 minutes.

2 mgm. Cardaissin accelerated the heart rate 18 beats and lasted 18 minutes.

4 mgm. Cardaissin accelerated the heart rate 24 beats and lasted 27 minutes.

6 mgm. Cardaissin accelerated the heart rate 30 beats and lasted 36 minutes.

In man the respirations were increased, as is shown in Table III. Cardaissin had no effect on the urine qualitatively or quantitatively. The temperature remained normal. There was no local reaction at the site of injection. There were no symptoms except that the cheeks became flushed and there was a slight feeling of exhilaration.

RESULTS

Since both Cardaissin and adrenaline are obtained from extracts of the suprarenal gland, it is of interest to compare the physical and physiological properties of these two substances.

Cardaissin is quite soluble in water, alcohol and acetone, whereas adrenaline is only slightly soluble in water and practically insoluble in organic solvents such as acetone and alcohol (Barger, 1914).

While Cardaissin accelerates the rate of the isolated heart for a considerable length of time, depending on the dosage, the

action of adrenaline is for a limited period rarely exceeding five minutes (Woods, 1912).

When Cardaissin is injected into the vein of a rabbit the heart rate is accelerated, the acceleration varying according to the dose; on the other hand, the intravenous injection of adrenaline slows the heart (Oliver and Schäfer, 1895).

Gunn (1914), employing the perfusion method and the isolated organ of the rabbit or cat, found that adrenaline will not revive a heart brought to a complete standstill by chloroform, whereas Cardaissin does revive a heart stopped by chloroform.

When Cardaissin was injected into the ear vein of rabbit No. R-7, the respirations were increased in rate; adrenaline, on the contrary, causes some diminution in the depth of the respirations and frequently causes apnoea (Oliver and Schäfer, 1895). Nice and others, however, have reported acceleration.

In regard to the action of Cardaissin on the blood vessels, it did not cause a ring of cat's aorta to contract nor did it constrict the small arteries and arterioles of the rabbit's ear. Mac-William showed that adrenaline causes a ring cut from a large artery to contract, and Auer and Meltzer (1917) have shown that the injection of adrenaline solution constricts the blood vessels of the ear. Cardaissin does not constrict the blood vessels, while adrenaline does.

Adrenaline causes inhibition of both the rhythmic movements and the tonus of the intestinal plain muscle (Boruttau, 1899). This is used as one of the most delicate physiological tests for its presence in any fluid. Hoskins (1911) got inhibition of a piece of rabbit's intestine with a solution of 1 in 400 million, and Stewart and Rogoff (1919) with 1 in 800 million. Cardaissin, however, failed to inhibit the normal tonus and rhythmic movements of the intestine.

Cardaissin did not stimulate nor did it inhibit the non-pregnant cat's uterus. It did not inhibit the gall bladder. It did not make an isolated strip of spleen contract. Cardaissin has no effect on smooth muscle. Adrenaline inhibits all movements of the non-pregnant cat's uterus (Dale, 1906), and of the gall bladder (Sharpey-Schafer, 1924). As observed by Oliver and Schäfer (1895) the spleen is one of the organs most sen-

## NEW CARDIAC ACCELERATOR

TABLE III  
THE EFFECT OF CARDIASSIN ON THE HEART RATE OF A NORMAL MAN.  
MAN, NO. M. 25. MALE, WHITE, AGE 31, SEATED. WEIGHT 90 KILOS. HYPODERMIC INJECTIONS. SEPTEMBER 12TH, 1926.

Time	Rate	Accel.	Resp.	Remarks			Remarks			
					P.M.		Time	Rate	Accel.	Resp.
7.30	84	0	17		9.30	84		0	17	
7.32	84	0			9.32	84		0	..	
7.34	82	0			9.34	84		0	17	
7.36	82	0			9.36	84		0	..	
7.38	84	0			9.38	84		0	..	
7.40	84	0			9.40	84		0	17	
7.42	82	0			9.42	84		0	..	
7.44	84	0			9.44	84		0	17	
7.46	82	0			9.46	84		0	..	
7.48	82	0			9.48	84		0	17	
7.50	82	0			9.50	84		0	..	
7.51	82	0			9.51	84		0	..	
7.52	84	0			9.52	84		0	..	
7.53	84	0			9.53	84		0	..	
7.54	86	2	22		9.54	90		6	20	
7.55	88	4	26		9.55	92		8	21	
7.56	91	10	28		9.56	98		12	21	
7.57	96	12	..		9.57	98		13	28	
7.58	96	12	..		9.58	100		16	..	
7.59	94	10	..		9.59	102		18	..	
8.00	90	6	26		10.00	102		18	30	
8.01	88	4	22		10.01	102		18	..	
8.02	86	2	18		10.02	100		16	28	
8.03	82	0	..		10.03	100		16	..	
8.04	84	..	..		10.04	98		14	22	
8.05	84	..	..		10.05	92		8	..	
8.06	82	..	..		10.06	90		6	18	
8.07	82	..	..		10.07	98		4	..	
8.08	82	..	..		10.08	94		0	17	
8.09	82	..	..		10.09	84		0	..	
8.10	82	..	..		10.10	84		0	..	
8.11	82	..	..		10.11	82		0	..	
8.12	82	..	..		10.12	80		0	..	
8.13	84	..	..		10.14	82		0	..	
8.14	84	..	..		10.16	84		0	..	
8.15	82	..	..		10.18	84		0	..	
8.16	82	..	..		10.20	82		0	17	

ABBREVIATIONS  
Rate—Heart Rate.  
Accel.—Acceleration of Heart Rate.  
Resp.—Respirations.

sitive to adrenaline. It contracts enormously with moderate doses and very distinctly with minute doses.

The intravenous injection of adrenaline provokes retraction of the nictating membrane, elevation of the eyelid, exophthalmos and dilation of the pupil (Lewandowsky, 1898). Cardaissin has no such effects.

Secretion of saliva from the submaxillary gland is produced by the intravenous injection of adrenaline, similar to that caused by excitation of the cervical sympathetic. It causes an abnormal flow in the cat (Langley, 1901). Cardaissin does not increase the salivary secretion of a normal cat.

According to Schafer and Herring (1906) adrenaline has a marked effect on urinary excretion and the kidneys. Cardaissin has not.

In man the subcutaneous injection of 0.5 to 1.5 mgm. of adrenaline causes within a few minutes pallor of the face and extremities, produced by peripheral vaso-constriction (Laroche and Richard, 1921). Cardaissin causes the face to become flushed and gives no signs of vaso-constriction.

Blum (1901) found that if adrenaline was injected subcutaneously, it caused glycosuria. Cardaissin does not.

Cardaissin and adrenaline differ in their physical and physiological properties with the exception that they both accelerate the isolated heart.

#### DISCUSSION

The results reported here probably do not warrant a full discussion; however, it might be well to say a few words regarding the preliminary augmented effect of Cardaissin. Apparently the first dose injected into an animal accelerates the heart rate far more than do succeeding doses. A possible explanation is that the Cardaissin stimulates the medulla of the suprarenal gland, thus augmenting the effect caused by the injection. The vacuolation of the adrenal medulla by an overdose tends to corroborate this hypothesis.

That Cardaissin is fairly pure is demonstrated by its constant physiological action. Fortunately, also, it can be sterilized and, so far as can be judged by one experiment, is quite safe to use in man.

## SUMMARY

1. A new substance called Cardaissin has been extracted from the suprarenal gland.
2. The method of extraction is briefly described.
3. It accelerates the heart rate. It does not affect any other organ with the possible exception of the adrenal medulla.
4. Cardaissin and adrenaline differ in their physical and physiological properties except that both accelerate the rate of the isolated heart.
5. Cardaissin, while markedly accelerating the heart in the absence of salts, heat or oxygen, cannot take the place of these essentials for muscular activity.
6. Cardaissin counteracts the cardiac depressant action of chloroform, morphine, strychnine and pilocarpine.
7. The minimal dose varies in different animals, probably increasing with their weights.
8. By means of fractional injections at properly timed intervals, Cardaissin can be used to accelerate the heart moderately over long periods of time.
9. A single large dose accelerates the heart rate to a fatal extent.
10. Cardaissin accelerates the heart rate of man. It has no harmful effects (one case).

I wish to take this opportunity of thanking President Murray and the Board of Governors for their hospitality in allowing me to do this research at the University of Saskatchewan; Dr. T. Thorvaldson, Professor of Chemistry, for his sympathetic reception and many kindnesses; Dr. S. Hadwen, Professor of Animal Diseases, who kindly allowed me the free use of laboratory and animals; Dr. W. F. Emmons of Vancouver, B. C., for his technical advice during the earlier experiments, and Mr. Murdo Cameron of Regina, Saskatchewan, Canada, who has financed this research.

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CONTRIBUTION TO THE STUDY OF THE PANCREAS  
IN TUBERCULOSIS

THE PANCREAS AND TUBERCULOSIS: IN GUINEA-  
PIGS AND IN ALBINO RATS

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In the first study of the pancreas and tuberculosis, published in this Journal (1) it was brought to notice that the pancreas is seldom attacked by tuberculosis infection in guinea-pigs or in cattle, even when the spleen, liver, lungs and other organs are infected. In the conclusions it was stated that the pancreas seemed to have a defensive agent or agents of its own secretion that hydrolyze then saponify the waxy or protective coating of the tubercle bacillus; that one of the defensive agents is steapsin or lipase; that endocrine agencies may also help to destroy the tubercle bacillus. These deductions were drawn from a former study (2) in which it was pointed out that a filtrate from an extract of pancreas containing lipase with the accompanying hormones to a small extent, was a hydrolyzer of the waxy or fatty coating of the tubercle bacillus when tested in vitro; the time required to accomplish this was proportional to the concentration of the lipase in the filtrate. Since the date of that publication a more concentrated lipase has been secured that acts quicker and without a co-hydrolyzer. The following is done to obtain a good test: A suspension of tubercle bacilli, free from clumps, say five cc. of suspension, is poured into an Erlenmeyer flask; the filtrate is alkalinized immediately before using to the degree usually found in nature when the bile mixes with the pancreatic juice before attacking fats of food; by test the Ph. value is 8.17; five cc. of the alkalinized filtrate is poured into the Erlenmeyer flask; the mixture is well shaken; after one-

half minute a loopful of this mixture is smeared on a slide and examined; no acid-fast rods are found—if the filtrate is properly prepared, its physical chemistry respected and the alkalinization properly done, either with bile salts or with carbonate or bicarbonate of sodium. If this mixture is kept from two to four hours then injected into guinea-pigs, the animals escape infection. The suspension of tubercle bacilli not treated with the lipase, when examined, shows numerous tubercle bacilli present.

Guided by the effect of the lipase on the tubercle bacilli the idea was conceived that if pancreatic deficiency is the cause of development of tuberculous infection in the living being, then an artificial supply or replenishment of lipase in the living being should act as a preventive of tuberculosis. Accordingly, one hundred guinea-pigs were given weekly injections of the alkalinized filtrate of lipase, 1 cc. at a dose, during a period of from eight to ten months; the effectiveness *in vitro* of the filtrate used was unquestionable when tested as explained.

A test was then made to find out how much this artificial replenishment of lipase reacted on injections of tubercle bacilli into animals. January 23, 1926, all these guinea-pigs that had had injections of the filtrate, as well as an additional hundred guinea-pigs not so injected with lipase, were put to the test. The two hundred guinea-pigs were injected with an emulsion from a lymphatic gland degenerated with tuberculosis; the gland was taken from a reactor cow "condemned" for tuberculosis.

Some of the animals were injected intra-abdominally, others hypodermically, on the inner side of the thigh, and still others intra-tracheally by way of the nasal passages. A few days after these injections a number of guinea-pigs died; it was found that the tissue emulsion contained bacteria and that these were germs of hemorrhagic septicaemia. An autogenous bacterin was made of these organisms; all the remaining guinea-pigs were injected with the bacterin, 1 cc. being the dose used. All the animals injected intra-abdominally died, and the rest looked as if they could not survive; but some recovered from the hemorrhagic septicaemia; in due course of time some began to show infection with tuberculosis. Bearing in mind the resistance of the pancreas to tuberculosis the pancreases of the autopsied guinea-pigs were weighed. The spleen was also weighed in some cases; the spleen in a normal guinea-pig should weigh less than the pan-

creas. But in acute infections the spleen becomes enlarged; this is especially well marked in tuberculosis.

A search in the literature was made to find some data on the status of the pancreas as regards its weight; little information was found; Gray's Anatomy, 21st edition, p. 1209, states that the human pancreas varies from 60 to 100 grams; Mathews Physiological Chemistry, 3d edition, p. 390, states that in the human adult the pancreas weighs about 87 grams. An exhaustive study of organ weights of normal rabbits covers a period of many years and was made at the Rockefeller Institute (3). Various organ weights are given; the spleen, liver, lungs, brain, kidneys, even of the deep cervical lymph nodes, mesenteric lymph nodes, hypophysis, pineal gland and others; but the pancreas is not mentioned.

In this study the weight of the pancreas in relation to the body weight seems to be of essential importance as will be shown below; there seems to be an intimate relationship between the weight of the animal's body and that of its pancreas,—as regards the animal's susceptibility to tuberculosis; an adequate pancreas seems to go hand in hand with lipase sufficiency in the tissues; this lipase sufficiency acting as a protective agent of the animal against infection with tubercle bacilli. It goes without saying that a large pancreas must also be of good functional activity.

Table No. 1 gives weights of the pancreas of a few of the control guinea-pigs that survived infection with hemorrhagic septicaemia but later developed tuberculosis; in the table the avenue of infection is designed "thigh," or "trachea."

TABLE I

Table No. I—Guinea-Pig Controls that Died of Tuberculous Infection. Series of January 23, 1926.

No.	Body Weight Grams	Site of Infection	Pancreas Weight in Grams	Spleen
				Weight Grams
1	605	? .....	0.907	10 times normal size
2	510	Thigh .....	1.201	5 times normal size
3	795	Thigh .....	1.410	5 times normal size
4	595	Thigh .....	0.800	6 times normal size
5	536	? .....	1.395	4 times normal size
6	680	Thigh .....	1.550	3 times normal size
7	686	Thigh .....	1.560	5 times normal size

No.	Body Weight Grams	Site of Infection	Pancreas Weight Grams	Spleen Weight Grams
8	953	Thigh .....	1.510	4 times normal size
9	800	?	1.520	4 times normal size
10	757	Thigh .....	2.450	4 times normal size
11	780	Thigh .....	1.212	5 times normal size
12	526	Trachea .....	0.421	20 times normal size
				severe case
13	890	Thigh .....	1.901	4 times normal size
14	797	Trachea .....	1.570	?
15	665	Trachea .....	1.575	?
16	550	Thigh .....	0.900	enormous size
				severe case
17	532	Trachea .....	0.950	6 times normal size
18	542	Trachea .....	1.120	6 times normal size
19	750	Trachea .....	1.365	4 times normal size
				severe infection
20	765	Thigh .....	2.020	mild infection
21	680	Thigh .....	1.900	3 times normal size
				mild infection
22	690	Thigh .....	0.950	5.200 grams
				severe infection
23	755	Trachea .....	1.820	4.720 grams
24	975	Abdomen .....	1.800	5.200 grams
				severe case
25	690	Trachea .....	1.000	9.000 grams
				severe case
26	702	Trachea .....	0.900	9.000 grams
				severe case
27	747	Trachea .....	2.320	3.700 ; mild case
28	625	Thigh .....	0.785	8.820 ; severe case
29	890	Thigh .....	1.450	5.670 ; severe case
30	412	Thigh .....	0.335	8.850 ; severe case
31	470	Thigh .....	0.565	10.300 ; severe case
32	945	Thigh .....	1.310	4.310
33	700	Thigh .....	1.450	2.500 ; mild case
34	581	Thigh .....	0.850	7.250 ; severe case
35	467	Thigh .....	1.000	1.900 ; mild case
36	700	Trachea .....	0.910	4.550 ; severe case

The average weight of pancreas of these guinea-pigs is about 0.188 grams per 100 grams of animal.

Some of the controls escaped tuberculous infection; and control No. 40 was autopsied December 12, 1926, or almost eleven months after injection. The weights of the pancreases of these controls are given in table No. II.

TABLE II

Table No. II.—Controls that escaped tuberculous infection.

No.	Body Weight Grams	Site of Infection	Pancreas Weight Grams	Spleen Weight Grams
37	995	Trachea .....	7.120	0.500
38	880	Thigh .....	2.450	0.450
39	813	Trachea .....	3.170	1.210
40	1151	Trachea .....	9.655	0.955

The weight of the pancreas of guinea-pig No. 37 is large; that of No. 40 is unusually large.

A few more control guinea-pigs survived; they are well at the date of this writing.

The survival of the control guinea-pigs without showing any trace of tuberculosis in their organs brings us to the question of so-called "immune" guinea-pigs. Searching the literature on this subject we find little to help in this study. Krause (4) presents a detailed study, but his point of search is not similar to ours; the immunity studied here is that in relation to the pancreas and its weight in proportion to the animal's body. When we consider the weight of the pancreas of the guinea-pigs that escaped tuberculous infection, as will be shown in Table IV, the subject of the pancreas and its weight in relation to body weight appears to be important. But before citing that table it is well to consider a group of guinea-pigs of this series that is intermediary between the severely infected controls, cited in Table I, and those of the animals that completely escaped tuberculous infection, or the so-called "immune" guinea-pigs, cited in Table No. IV.

TABLE III

Table No. III.—Guinea-Pigs; Series of January 23, 1926. These animals had had weekly injections of lipase filtrate during a period of from eight to ten months, then were infected with tissue emulsion from a reactor cow that was also a carrier of hemorrhagic septicaemia; the animals survived infection with hemorrhagic septicaemia but died of tuberculous infection.

No.	Body Weight Grams	Site of Infection	Pancreas	Spleen
			Weight Grams	Weight Grams
1	910	Trachea .....	1.900.....	Large
2	690	Trachea .....	1.460.....	Large
3	975	Trachea .....	2.700.....	Large
4	870	Trachea .....	2.000, mild case.....	?
5	735	Trachea .....	1.450.....	?
6	927	Trachea .....	2.152.....	?
7	757	Trachea .....	1.610.....	?
8	800	Thigh .....	2.170.....	?
9	912	Thigh .....	1.720.....	?
10	815	Thigh .....	1.955.....	?
11	770	Thigh .....	3.350.....	?
12	665	Thigh .....	1.390.....	?
13	835	Thigh .....	1.400.....	?
14	660	Thigh .....	1.000.....	?
15	652	Thigh .....	1.180.....	?
16	909	Thigh .....	2.225.....	?
17	820	Thigh .....	1.520.....	?
18	940	Thigh .....	2.480.....	?
19	910	Trachea .....	2.820, mild case.....	1.670
20	1110	Trachea .....	2.835, mild case.....	2.630
21	875	Thigh .....	1.750.....	?
22	632	Thigh .....	0.850, severe case.....	7.560
23	687	Thigh .....	1.410, severe case.....	6.000
24	942	Thigh .....	1.900, severe case.....	5.500
25	785	Trachea .....	2.790, mild case .....	5.820

The average weight of pancreas per 100 grams of body weight of these guinea-pigs is about 0.233 grams.

We have now come to the group of guinea-pigs that had had injections of lipase and escaped infection with tuberculosis. Tissue emulsion from some of the autopsied animals was injected hypodermically into control guinea-pigs; these controls are alive and apparently well at the date of this writing. Table IV shows the weights of the pancreas and body of this group.

TABLE IV

Table No. IV. Guinea-pigs; Series of January 23, 1926. These animals had had weekly injections of 1 cc. of filtrate of lipase during a period of from eight to ten months; they were then injected with tissue emulsion from a reactor cow "condemned" for tuberculosis; this cow was also a carrier of hemorrhagic septicaemia. The guinea-pigs were severely infected with hemorrhagic septicaemia but escaped infection with tuberculosis.

No.	Body Weight, Grams	Site of Injection	Pancreas	Spleen
			Weight, Grams	Weight, Grams
1	1090	Trachea.....	5.520.....	No record
2	1236	Trachea.....	4.425.....	0.855
3	1270	Trachea.....	6.500.....	1.300
4	1125	Thigh.....	3.600.....	2.640
5	972	Trachea.....	3.860.....	1.290
6	1111	Trachea.....	5.600.....	1.400
7	1196	Trachea.....	4.595.....	1.060
8	1068	Thigh.....	5.035.....	1.470
9	855	Thigh.....	2.570.....	1.940
10	1180	Trachea.....	4.400.....	0.700
11	901	Trachea.....	3.620.....	1.260
12	912	Trachea.....	3.400, pneumonia.....	2.220
13	772	Trachea.....	6.000 *.....	0.760

\* Died while giving birth to her four young.

The average weight of pancreas in this table is about 0.431 grams per 100 grams of guinea-pig.

Reviewing the weights of pancreases presented in the tables, we have the following: The controls that died of severe tuberculous degeneration of their organs show an average of 0.188 grams of pancreas per 100 grams of body weight; the intermediary

group of animals, that had had injections of lipase previous to the infection, show an average of pancreas weight of 0.233 grams per 100 grams of body weight; the tuberculous degeneration of this group was less marked as compared with the severe tuberculous degeneration found in the controls autopsied at about the same time; while the group of guinea-pigs that had had lipase injections and escape tuberculous infection showed an average weight of pancreas of about 0.431 grams per 100 grams of body weight.

Work is yet to be done to determine the rôle played by the injections of lipase during a prolonged period of time: do these injections act simply as replenishers of lipase content in the tissues? Do they stimulate the pancreas to more energetic functions as regards the lipase output? Is such stimulated production of lipase started in the tissues themselves?

#### TUBERCULOSIS IN THE ALBINO RAT

The study of tuberculosis in the albino rat seems to confirm the correlation of the pancreas and tuberculosis. It has been difficult to obtain all the literature on tuberculosis in the albino rat; but the work of Gloyne and Page (5) presents a scholarly study of the question; it shows that this animal does not contract tuberculosis; but tissue emulsion from such injected albino rats causes tuberculosis in the guinea-pig. Ornstein and Steinbach (6) repeated the above tests and confirm the results. Our tests were made August 9, 1926; a number of albino rats were injected hypodermically, on the inside of the thigh, with 1/10 milligram of virulent bovine tubercle bacilli; twenty guinea-pigs were similarly injected as controls; the puncture made by the hypodermic needle quickly healed in the albino rats; but all the guinea-pigs developed tuberculous ulceration and suppuration at the site of injection; the suppuration persisted in spite of repeated daily irrigations with carbolic acid solution; all the guinea-pigs developed severe generalized tuberculosis; but the albino rats did not show any evidence of tuberculous infection. Sections of their tissues were made by the assistant pathologist of the Colorado Agricultural College, Fort Collins, Colorado. Dr. William H. Feldman; his findings agree with those of Gloyne and Page. Table No. V presents the weights of the pancreas and body of some of the injected albino rats of our series.

TABLE V

Table No. V. Albino rats, males, series of August 9, 1926, injected hypodermically, on the inside of the thigh, with 1/10 milligram of tubercle bacilli, virulent bovine type. Chloroformed November 20, 1926.

No.	Body Weight, Grams	Pancreas Weight, Grams	Spleen Weight, Grams
11	167.....	0.585.....	0.495.....
12	105.....	0.485.....	0.565.....
13	197.....	0.640.....	0.730.....
14	195.....	0.830.....	0.720.....
15	232.....	0.770.....	0.830.....
16	147.....	0.680.....	0.630.....
17	140.....	0.555.....	0.630.....
18	228.....	0.870.....	0.850.....
19	224.....	0.825.....	0.840.....
20	229.....	0.885.....	0.840.....
21	230.....	1.400.....	0.740.....
22	195.....	0.650.....	0.690.....
23	221.....	0.840.....	0.630.....
24	193.....	0.800.....	0.600.....
25	200.....	0.800.....	0.705.....
26	205.....	0.885.....	0.675.....
27	217.....	1.900.....	0.755.....
28	212.....	0.810.....	0.710.....
29	190.....	0.755.....	0.705.....
30	200.....	0.820.....	0.750.....
31	205.....	1.850.....	0.710.....

The average pancreas weight is about 0.451 per 100 grams of body weight.

Compare the weight of the pancreas of these albino rats with the weight of the pancreas of the control guinea-pigs that died with severe tuberculous degeneration; the average weight of pancreas in those guinea-pigs is about 0.188 grams per 100 grams of body weight; but in the albino rats, that are immune to tuberculous infection, we find an average of about 0.451 grams of

pancreas per 100 grams of body weight; it seems logical to think that the pancreas—its weight and its functional performance—is intimately related to the reaction to the tubercle bacillus in the living being.

We claim, on the strength of the facts adduced here, that the lipase in the tissues and the pancreas is a factor, if not the chief factor, in preventing the tubercle bacillus from infecting the albino rat; the supply of lipase in this animal is apparently of sufficient amount and steady supply to affect adversely the protective coating of the tubercle bacillus. The bacillus remains acid-fast, but it does not cause infection; the logical conclusion seems to be that the tubercle bacillus in the albino rat is comparable to the attenuated tubercle bacillus; such a bacillus is acid-fast, but remains harmless in some animals. In our own experience we "lost" several large series of guinea-pigs injected with tubercle bacilli that were supposed to be virulent, but were attenuated bacilli. Our guinea-pigs escaped infection.

The difference between the attenuated tubercle bacillus in the cultures as above related and that in the albino rat is the following: In the albino rat the bacillus is maintained attenuated; and it is maintained so apparently by the lipase in the tissues; but as soon as the bacillus is injected into the highly susceptible guinea-pig, with its natural pancreatic deficiency—in the majority of cases—the bacillus gathers strength and causes tuberculosis in the guinea-pig.

In guinea-pigs there is a marked fluctuation in the weight of the pancreas of different animals: Compare the weight of pancreas of Table No. I, about 0.188 grams; that of Table No. II, about 0.233 grams, and that of Table No. IV, about 0.431 grams. But this fluctuation of pancreas weight does not seem to exist in the albino rat; for the sake of comparison a table of weights of pancreas of a few normal female rats is given below:

TABLE VI

Table No. VI. Normal Albino Rats, Females; Separated from the Males about Four Months.

No.	Body Weight, Grams	Pancreas Weight, Grams	Spleen Weight, Grams
32	200	0.800	0.970
33	173	0.560	0.670
34	145	0.545	0.520
35	173	0.760	0.580
36	145	0.640	0.580
37	184	0.650	0.610
38	167	0.580	0.580
39	156	0.650	0.600
40	147	0.500	0.800
41	162	0.695	0.725
42	163	0.730	0.625
43	136	0.560	0.505
44	164	0.980	0.610
45	164	0.650	0.600
46	170	0.560	0.580
47	133	0.650	0.320
48	151	0.840	0.610
49	158	0.820	0.650
50	140	0.660	0.640
51	160	0.850	0.590
52	150	0.840	0.650
53	166	0.570	0.440
54	159	0.570	0.370
55	140	0.540	0.385
56	136	0.600	0.485
57	158	0.550	0.530
58	136.5	0.590	0.320
59	131.5	0.590	0.320
60	141.5	0.530	0.510
61	191.5	1.100	0.850

The average weight of pancreas of these female albino rats is about 0.429 grams per 100 grams of body weight.

#### CONCLUSIONS

1. In a previous study of the pancreas and tuberculosis, published in this journal, it was brought to notice that it was a rare thing to find the pancreas infected with tuberculosis.

2. The defensive agent of the pancreas against tuberculosis seemed to be the lipase of the pancreas.

3. Guinea-pigs injected with emulsion of tubercle bacilli reacted in different ways: those that had a pancreas of small weight in relation to their body weight succumbed to severe tuberculous infection; but a marked percentage of the guinea-pigs that had a larger pancreas escaped infection.

4. The control guinea-pigs that succumbed had about 0.188 grams of pancreas per 100 grams of body weight; while those that escaped infection showed 0.431 grams of pancreas per 100 grams of body weight.

5. The guinea-pigs with the larger pancreas had weekly injections of lipase. To what extent these lipase injections acted as a preventive of infection is to be studied later.

6. We made tests of injecting albino rats with tubercle bacilli; our results are similar to those obtained by other workers: The albino rats did not contract tuberculosis.

7. The albino rat has a large pancreas,—about 0.451 grams per 100 grams of body weight in animals examined by us; in the females examined we found 0.429 grams of pancreas per 100 grams of body weight.

8. We believe that the albino rat is protected against infection with tuberculosis by virtue of a large amount of lipase in its tissues.

9. The tubercle bacillus remain acid-fast but harmless in the albino rat, probably because the lipase sufficiency in its tissues maintains the germ in an attenuated form.

Dr. Robinovitch takes great pleasure in expressing her thanks to the chief of field work, U. S. Bureau of Animal Industry, Dr. W. E. Howe, for supplying her with the pancreas glands used in these tests.

She also feels deeply indebted to the president of the School of Mines, Dr. M. F. Coolbaugh, for granting her facilities at the school needed in her research.

She feels indebted to Dr. William H. Feldman for making a pathological study of the tissues of the albino rats.

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## Book Reviews

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THE ENDOCRINE ORGANS. 2nd. ed. Part II. Sir E. Sharpey-Schafer, 1926. Longmans, Green and Co., Ltd., London, pp. 177-418.

For anyone who is familiar with the first edition of this well known treatise or with Part I of the second edition, a mere announcement of the appearance of this volume will suffice. For clarity of style, inclusiveness of scope, balance and timeliness this work is the most satisfactory treatment of Endocrinology in the English or perhaps any other language.

The text is divided into 36 lectures covering the pituitary and pineal glands, the alimentary canal, the pancreas and the sex glands.

The illustrations are plentiful and well selected. The bibliography is remarkably complete for a book of this size and is thoroughly cosmopolitan. Convenience is subserved by printing the references, often annotated, as foot notes. The occasional use of the form "op. cit.," however, rather than repetition of the reference is somewhat annoying to the reader, who must thumb back to pick up the original.

A four-page preface serves to correct certain mistakes in Part I and to add various important data that have appeared since the publication of that Part.

THE THYROID GLAND. Charles H. Mayo and Henry W. Plummer, 1925. The C. V. Mosby Co., St. Louis, pp. 83.

This book is made up of the two Beaumont Foundation lectures for 1925 (Detroit). The first lecture—on goiter—by Dr. Mayo is a compilation that is valuable chiefly as indicating what data this well known authority considers most important. Otherwise it embodies little that is not to be found as well presented in several previous works. The most satisfactory section is the historical introduction. It appears that the operative treatment of goiter began considerably earlier than is usually recognized. There were 126 cases known up to 1861.

Dr. Plummer's lecture on "The Function of the Thyroid Gland" is a much more original work. He develops in a fascinating way the conceptions which finally led him to institute the iodine treatment of exophthalmic goiter. His main thesis

is that "Thyroxin is active in nearly all or all the cells of the body" and that it is "a catalytic agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cells." The liberty thus taken with the language of physical chemistry is unfortunate, but otherwise the whole lecture is admirable. It is pithy and notably practical. The danger is failing to make a proper differential diagnosis between true hyperthyroidism and exophthalmic goiter is stressed and the differential points clearly emphasized. For anyone having to deal with the treatment of goiter patients this lecture is the most worth-while single article known to the reviewer.

GOITER AND OTHER DISEASES OF THE THYROID GLAND. Arnold S. Jackson, 1926. Paul B. Hoeber, Inc., New York, pp. 350.

One surmises that the author has set out to put as much practical information as possible into 350 pages. The first 50 pages are rather negligible, amounting to a patchy, inadequate treatment of such topics as anatomy, physiology, geographical distribution, etc.

Beginning with the chapter on classification and diagnosis, the book becomes much more satisfactory. The author frankly states that the work is colored by three years' experience at the Mayo Clinic, but it contains much that is based on personal experience. That there existed any pressing need for another book on goiter is doubtful, but, having been written, it can be recommended as a valuable addition to the list. It is clear in style and well illustrated, mostly with photographs. The various operative procedures are especially well pictured.

The book closes with a good ten-page bibliography and excellent indexes.

## Abstract Department

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### Relation of epinephrine response to temperature and rhythmic vigor.

Barlow (O. W.) & Sollmann (T.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1926, **28**, 325-339.

Increased temperature of the perfusate increases the rate and amplitude of the perfused frog heart. The response to epinephrine, within limits, increases with temperature, in a relation which the authors term "augmented summation." This response is not due to increased reaction velocity but to increased excitability of the heart.—C. I. R.

### The effect of adrenalin administered orally.

Brems (A.), *Acta med. Scand.* (Stockholm), 1926, **64**, 69-90; *Abst. Chem. Absts.* **20**, 3743.

Adrenalin administered orally in 4 mgm. doses produces a marked rise in blood sugar, but fails frequently to cause a rise in the blood pressure. Not infrequently it actually causes a drop in pressure.

### Studies on the conditions of activity in endocrine glands. XX. The influence of motion and emotion on medulliadrenal secretion.

Cannon (W. B.) & Britton (S. B.), *Am. J. Physiol.* (Balt.), 1927, **79**, 433-465.

The evidence for and against emotional stimulation of medulli-adrenal secretion is reviewed and the desirability of securing further evidence is made clear. The advantages of the lasting preparation of the denervated heart are pointed out: the acceleration is slight (about 10 beats per minute or fewer), if thyroid, hepatic and medulliadrenal factors are excluded; the faster heart beat which occurs when medulliadrenal secretion alone is admitted to action and is stimulated justifies the use of the heart as an indicator of an increase of that secretion; the denervated heart permits a graphic record to be made which displays the latent period, the peak of activity, and the gradual subsidence of the humoral response; the observations may be repeated again and again on the same animal under normal conditions; control test can be made on the same animal after inactivation of the adrenals by removal of one and denervation of the other; and, the increased heart rate can reasonably be interpreted as a rough measure of the increase of adrenin in the blood, for the faster circulation which would accompany in-

creased secretion of adrenin would be unfavorable rather than favorable to its causing the cardiac acceleration. Minor movements of the cat with denervated heart, such as extending the legs or turning the body, were accompanied by increases of heart rate of 5 to 10 beats per minute; walking made the rate faster by 10 to 20 beats. The average increase in 27 tests was 15. No signs of emotional disturbances were noted. After adrenal inactivation the same activities were accompanied by very slight acceleration or none at all—the average in 23 tests was 1 beat per minute. Emotional excitement, such as may be aroused by bringing near the cat a barking dog, or by restraining the animal in a holder, and manifested by erection of hairs and minor movements (e. g., hissing, snarling, retraction of the ears, baring of the teeth, or restless twitching of the tail) was accompanied by a faster heart rate. The increment varied roughly between 15 and 30 beats in the presence of the barking dog and between 10 and 35 beats during restraint in the holder. The average rise in 45 tests was 22. The variations of rate corresponded with variations in other signs of emotional reaction. After inactivation of the adrenal glands repetition of the same conditions with the same animals induced only minor accelerations, or none at all, or, in some instances, a small decrease of heart rate. The average in 39 tests was 2. Great emotional excitement plus vigorous activity, brought about by letting a dog bark at the cat when caged, or by causing the cat to struggle in the holder, though it lasted only a minute or less, caused the heart rate to increase, in the former condition between approximately 40 and 80. The average rise in 53 tests was 49. After the medulliadrenal factor had been excluded, the rise of rate was usually 8 beats or fewer, and in some tests the heart worked more slowly after the struggle than before. The average rise in 43 tests was 5. After a cat has been caged and excited by a barking dog outside, the disturbance thus induced may persist for 20 or 25 minutes, although the animal meanwhile is resting quietly on a cushion.—Author's Abstract.

Studies on the conditions of activity in endocrine glands, XXI. The rôle of adrenal secretion in the chemical control of body temperature. Cannon (W. B.), Querido (A.), Britton (S. W.), & Bright (E. M.), Am. J. Physiol. (Balt.), 1927, 79, 466-507.

To indicate increased secretions of adrenin the completely denervated heart was employed. Since the thyroid gland and the liver were likewise denervated, the adrenal medulla alone was left as a factor capable of causing, humorally, a faster heart beat. The animals thus prepared lived normally in the laboratory. The first test applied was exposure of the animals to a cold environment. Under these conditions, with no emotional element or struggle involved, the rate of the denervated heart increased between 18 and

33 per cent. After the right adrenal gland was removed and left was wholly denervated, the same test on the same animals caused the heart rate to decrease. The second test was the establishment of a heat debt by introducing a known amount of cold water (between 0° and 1°) into the stomach—a method which is easily available at any time and, with fairly uniform environmental temperature, is satisfactorily quantitative. The heat debt established in cats varied between approximately 1500 and 2000 small calories per kilo. There was an initial disturbance of the heart rate due to giving the water, but after that subsided to a plateau, the elevation of rate ranged between 23 and 28 per cent. This increased heart rate may continue for an hour or more. When equal amounts of warm water (between 31° and 34°) were given, the increased rate disappeared in fifteen minutes or less. After the adrenal glands had been rendered inactive the test with cold water on the same animals caused only slight acceleration and in some instances depression of the heart rate. From these observations the conclusion is justified that conditions which would naturally cause a lowering of body temperature induce an increased discharge of adrenin into the circulation. The evidence that secreted adrenin has a calorogenic action is reviewed and two types of experiment are proposed to demonstrate its service to the organism—a, its relation to shivering, and b, its effect on metabolism in the absence of shivering. When the heat debt is large (1000 small calories per kilo or more, with the water at 1°) and the room temperature is about 20° it is commonly met by two calorogenic agencies—increased output of adrenin and shivering. Although shivering coincides with the period of greatest medulliadrenal discharge, it is not a necessary condition for the discharge—it may be wholly absent though the heart rate is well accelerated. If in an environmental temperature of about 20° a heat debt of only 900 calories is to be paid, shivering occurs; and if it occurs, it is of short duration (3 minutes). If now, the adrenal glands are put out of function, and a heat debt of 900 calories is established, shivering almost uniformly occurs and may last for as long as 17 minutes. Thus when the heat-producing service of the adrenal medulla is lacking, the shivering mechanism is resorted to. Establishing a heat debt averaging 449 small calories per kilo caused in 22 observations on 11 human subjects, an average maximal increase of metabolism of 16.4 per cent, with variations ranging upward as high as 38 per cent. These increases were not accompanied by shivering. The development of the peak of the metabolic rate averaged 23 minutes after the cold water was taken, and therefore was not due to the disturbance of taking the water. When an equivalent amount of warm water was taken the average increase of metabolism was only 3.1 per cent, and since the time of maximal increase occurred regularly in the first seven minutes of the experiment, it must have

resulted chiefly from the disturbance of taking the water. In one of our cases regularly and in others occasionally the heat debt induced a preliminary fall of metabolism which was followed by a rise often to a level well above that of the preliminary basal period. When shivering occurs it usually causes a marked and sudden increase of the metabolic rate, which may be as much as 60 or 90 per cent above the basal. In cold surroundings a given heat debt causes a much greater increase of metabolism than in warm surroundings. These experiments have shown that the same conditions which increase adrenal secretion in lower animals increase metabolism in man, and this without shivering. It is concluded, therefore, that a disturbing heat loss evokes activity of the adrenal medulla and that the extra output of adrenin by hastening combustion, serves to protect the organism against cooling. The experiments of Voit and Rubner and of their opponents are discussed in the light of these experiments. The experiments reported obviously have an important bearing on the long-waged controversy over the question of true chemical augmentation of metabolism. They support the contention of Voit and Rubner that such a process exists in the body and they account for the mode of action of that process.—Author's Abstract.

Adrenalin treatment of chorea minor (*Die hormonale Behandlung der Chorea minor*). Duzar (J.), *Monatschr. f. Kinderh.* (Leipz.), 1926, 31, 520.

Children were injected with adrenalin to note effect in different conditions. When given in conjunction with bicarbonate of soda it seems to help the alkaline phase of adrenalin action and also makes it easier to take. Improvement in chorea was noted when the adrenalin pressure effect wore off. The author cannot explain the effect of the adrenalin but thinks that it acts on the vegetative nervous system. He reports good results in a few days. His method is as follows: On the first day adrenalin chlorid, 1-1000 mgm. 0.1, diluted with 1 cc. of physiological salt solution, is very slowly injected intravenously; repeat in the afternoon. During the day sodium bicarbonate, five to six tablespoonsful, is given in the food. The same procedure is carried out on the second and third days. On the fourth day one intravenous injection is discontinued and instead one subcutaneous injection of 1 cc. adrenalin without saline is given in the afternoon and as improvement continues this is changed to two subcutaneous injections. The bicarbonate is continued throughout the treatment.—M. B. G.

Adrenalin tetany. Duzar (J.) & Hensch (W.), *Jahr. f. Kinderh.* (Leipz.), 1926, 64, 142-149.

Fourteen children between the ages of 12 and 14 years were studied. Intravenous injections of large doses of adrenalin alone

were followed by intense pallor, headache, decreased and then increased respiratory rate, nausea, coughing, salivation, increased blood pressure and bradycardia. No tetany was observed. Simple hyperventilation for 8 to 10 minutes produced tetany spasms in hands and fingers, carpopedal spasm, painful cramps, itching and sometimes opisthotonus. Facial tetany was one of the last symptoms to appear. The administration of adrenalin increased the action of the hyperventilation by causing the symptoms to appear earlier and stronger. The blood pressure was lowered by hyperventilation but increased by a subsequent injection of adrenalin. An injection of adrenalin following hyperventilation produced hyperglycemia in the majority of cases. The injection of adrenalin alone in latent idiopathic tetany without hyperventilation produced mild carpopedal spasms. The action of adrenalin cannot be explained entirely on the basis of a peripheral action. If hyperventilation tetany is produced by increased muscle tonus and increased by adrenalin, then this artificial tetany may be of some therapeutic value in conditions of pathologically changed muscular tone. This has been tried by the authors in chorea with good results. In chorea instead of hyperventilation, a similar situation was produced by the administration of large doses of sodium bicarbonate, which resulted in an alkalosis, and then adrenalin was administered. In place of tetany being produced there was an improvement in the pathological muscular tone and a resultant improvement in the chorea.—M. B. G.

**Adrenaline glucemia and respiratory metabolism.** Erichson (K.), Ztschr. f. d. ges. exper. Med. (Berl.), 1926, 50, 637-648; Abst., Chem. Absts. 21, 128.

The effect of adrenaline injected subcutaneously in 4 healthy men was indicated by an increase in consumption of oxygen and an increase in blood sugar. There was no parallelism between the increase of blood sugar following the injection of adrenaline and the respiratory quotient, as an expression of increased combustion of carbohydrates. In adrenaline glucemia there was no increase in acidity of the urine, indicating a combustion of carbohydrates. There was no increased carbohydrate combustion in adrenaline glucemia as in alimentary glucemia, and there is a similarity between adrenaline and alimentary glucemia only during the first hour, before alimentary glucemia from dextrose has brought about increased combustion of carbohydrates.

**Phenomena following suprarenalectomy in dogs.** Estrada (O. P.), Rev. de la Soc. Arg. de Biología, (Buenos Aires), 1926, 2, 348; Abst. J. Am. M. Ass., 86, 66.

The author observed the symptoms following the removal of

the suprarenals in dogs. An interval of from seven days to several months elapsed between the excision of the two glands. Local anesthesia with procaine hydrochloride and epinephrine proved excellent as to subsequent by-effects. In spite of repeated bleeding and various injections and manipulations, the animals lived from 30 to 136 hours. The earliest symptoms of suprarenal insufficiency, occurring a few hours after operation, hypoglycemia; then came loss of appetite and increase in blood volume and in temperature. The blood pressure remained about normal almost to the end. Digestive disturbances, vomiting, diarrhea, etc., belonged to the later stage. Behavior changes were observed, the animals gradually becoming docile and listless. Circulatory and nervous changes predominate when the survival is brief, and digestive and metabolic symptoms when it is otherwise. The necropsies showed congestion of the stomach, liver, spleen and especially the pancreas. The pancreatic congestion suggested a possible discharge of insulin.

**Inefficiency of pilocarpine upon energy metabolism in the absence of the suprarenal capsules.** Giaja (I.) & Chahovitch (X.), Compt. rend. Soc. de biol. (Par.), 1926, 182, 1292-1293; Abst. Chem. Absts., 21, 136.

Experiments with rats show that pilocarpine does not raise the basal metabolism of the decapsulated animal. In the normal rat pilocarpine causes an increase of 2 or 3 times the basal metabolism.

**Pathogenesis of death from burns.** Greenwald (H. M.) & Eliasberg (H.), Am. J. M. Sc. (Phila.), 1926, 171, 682.

Two clinical cases of burns with hypoglycemia are reported. Experiments on 10 rabbits were carried out to study the effects of superficial burns on the blood sugar content of organs concerned with carbohydrate metabolism. In rabbits the cause of death from burns may be divided into two stages: (1) The initial stage due to shock accompanied by high blood sugar content, due to hyperactivity of the adrenals; (2) Secondary stage due to degenerative changes, particularly in the suprarenals. The administration of adrenalin is to be restricted to the second stage of suprarenal exhaustion and is contraindicated in the first stage.—M. B. G.

**Internal secretion, basal metabolism and transformation of protein in pregnancy.** Klaften (E.), Arch. f. Gynaek. (Berl.), 1926, 129, 66-86; Abst. Chem. Absts., 20, 3783.

Extracts of the hypophysis exert the same effect on the metabolism of pregnant and non-pregnant women. Preparations of the anterior and posterior lobes of the hypophysis are antagonistic in action, the former decreasing and the latter increasing basal metabolism. Thyroid extract increases basal metabolism much more

in the pregnant than in the non-pregnant woman. As protein metabolism has been found to be increased in eclampsia these experimental studies afford a basis for thyroid treatment when eclampsia is impending. Placental extract increases metabolism but ovarian extract has little or no effect. In 10 women with extirpation of the uterus and ovaries or x-ray castration there was a decrease in basal metabolism.

**Adrenal hypertrophy in experimental uremia.** MacKay (E. M.) & MacKay (Lois L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 24, 128.

There was an increase in adrenal weight of 65 per cent in the male and 46 per cent in the female uremic white rats. This increase was in the cortex and due partly to an increased amount of water but largely to an increase in lipoids.—J. C. D.

**Compensatory hypertrophy of the adrenal cortex.** MacKay (E. M.) & MacKay (L. L.), J. Exper. Med. (N. Y.), 1926, 43, 395-402.

The object of the study reported in this paper was that of determining whether or not hypertrophy of one adrenal in the rat follows removal of the other. The method employed was that of determining the total weight and the relative amount of cortical and medullary tissue in the surviving adrenal forty days after operation. Twenty-five female albino rats, 93 days of age, were thus operated upon, and in an equal number of controls one of the adrenals was exposed. An adequate diet was provided and the weight curves for the two groups remained nearly alike. It was found that the surviving adrenal in the experimental animals hypertrophied 61 per cent on the average. This hypertrophy was shown to be due entirely to hypertrophy of the cortex without change in the size of the medulla.—I. McQ.

**Borderline forms of "interrenalism."** Mathias (E.), Zentralbl. f. Gynaek. (Leipz.), 1926, 50, 2489; Abst. J. Am. M. Ass., 88, 137.

Mathias suggests this term for the virilism induced by a certain kind of hypernephroma or increase in the number of cells of the suprarenal cortex. This effect of hyperplasia of the tissue of the suprarenal cortex may be seen not only in strictly pathologic conditions but in the growth of hairs on the chin in older women and in the slight virilism of pregnancy, evident in the physiognomy, in the increase of hair on the entire body, pigment changes, growth of beard, etc. He reproduces the photograph of a woman, 57 years old, with features of the masculine type and a strong growth of hair on the chin. On her death, from carcinoma of the uterus, the cortex of both suprarenals was found to contain a large number of small, globular adenoma nodules. The ovaries were atrophic.

Adrenalin and the tonus of decerebrate rigidity. Porter (E. L.), Am. J. Physiol. (Balt.), 1926, **78**, 495-499.

An artificially stimulated muscle, particularly if fatigued, shows marked improvement in contraction after intravenous injections of adrenalin (Gruber, 1922). In view of this fact it might be expected that a muscle in tonus would show similar improvement following adrenalin. It would appear probable that this would be most marked if the tonus were diminishing, i. e., fatiguing. A method is described of using a small extensor muscle of the tail in the decerebrate cat for testing the effect of adrenalin when the muscle is showing steadily decreasing tonus. Thirty-five experiments were made on some cats. Uniform results were secured. It was found that if this muscle be thrown into tonic contraction, and then its tonus allowed to diminish, there is no improvement in contraction following intravenous injections of adrenalin (in doses of 1 cc. of a 1:10,000 solution). It is concluded that this constitutes evidence that the tonic contraction of decerebrate rigidity is not brought about through sympathetic innervation.—R. G. H.

The effect of small amounts of adrenalin upon the glomerular blood vessels of the frog's kidney perfused at constant rate. Richards (A. N.), Barnwell (J. B.) & Bradley (R. C.), Am. J. Physiol. (Balt.), 1927, **79**, 410-418.

The kidneys of frogs have been perfused with frog's blood by means of an apparatus which insures constancy of blood flow. The addition of a small amount of adrenalin to the blood caused the perfusion pressure to rise and the glomerular tufts to swell. The result is interpreted as further evidence that the efferent vessel of the glomerulus is subject to the constricting action of adrenalin.  
—Author's Abstract.

Studies on adrenal insufficiency in dogs. I. Control animals not subjected to any treatment. Rogoff (J. M.) & Stewart (G. N.), Am. J. Physiol. (Balt.), 1926, **78**, 683-710.

This paper is a result of ten years of intensive study of adrenal deficiency. Hundreds of animals have been observed but this paper includes results in only certain dogs. Special skill in surgery is claimed. As a basis of comparison with dogs subjected to treatment, or pregnant, tables are given comprising the results of observations on 34 male dogs and 39 non-pregnant females. Another non-pregnant female has been added since, making a total of 74 controls. Pregnant animals are excluded from this control series, because, as was shown, the period of survival is markedly lengthened by pregnancy. The adrenals were removed in a two-stage operation, with an interval varying from about a week to about 6 months. An interval of a week was found to give as good

results as a longer one. The majority of the dogs (about two-thirds) lived 4 or 5 to 8 or 9 days after the second adrenalectomy. A fair number (about one-tenth) lived 10 to 12 days. Two dogs lived until the 15th day. About one-sixth of the animals survived 4 days or less. The animals recover rapidly from the second operation. It is a general rule that with the shorter times of survival the period of normal health and good appetite is relatively less than with the longer survival periods. It is a consequence of this that the time for which the dog still lives after the anorexia, the most characteristic and constant symptom, has declared itself is not very different in the great majority of the animals, whether the total survival period be long or short. Most of the dogs died in less than 3 days after definitely refusing food. Other symptoms (bilious vomiting, nervous symptoms, asthenia, etc.) are described. The pathological changes found at autopsy, especially in the gastro-intestinal tube (congestion and hemorrhage in the mucosa, blood in the lumen) and in the pancreas are indicated in the tables, and details are given in the protocols cited. It would seem from these studies that especial importance is to be ascribed to the gastro-intestinal disturbances in experimental adrenal deficiency and, by inference, in Addison's disease. This is reminiscent of Mann's earlier work on gastro-duodenal ulcers following adrenal deficiency. The authors definitely commit themselves to the intoxication theory of adrenal deficiency.—R. G. H.

**The relation of depressant and stimulant actions of epinephrine on the frog heart.** Sollmann (T.) & Barlow (O. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, 29, 233-255.

The authors believe the response of the frog heart to epinephrine, both by perfusion and by irrigation of isolated strips, to be the resultant of two opposing actions: (1) Stimulation of the accelerator receptive mechanism; (2) depression and injury of cardiac muscle. Both actions increase with the concentration of epinephrine. With solutions of concentration stronger than 1:1,000,000,000 the first effect predominates, the second with lower concentrations. The depressant effects are not antagonized by atropine or ergotoxine.—C. I. R.

**Effects of extracts obtained from the cortex of the suprarenals.** Vasarhelyi (B.), Magy. Orv. Arch. (Budapest), 1926, 27, 251-257; Abst. Chem. Absts., 21, 136.

Extracts made from the cortex of beef suprarenals with alcohol and water exert a faint vasoconstriction on the Laewen-Trendleburg preparation and are capable of increasing the work of the rabbit's heart in Locke's apparatus. As this effect is 10 to 20 times as great as would result from the adrenaline present, the action cannot

be due to adrenaline. The extracts are without effect on the carbohydrate metabolism of the surviving heart. The oxygen intake of muscles and liver increases; that of the brain and kidneys decreases under the influence of this extract. The cramps of pigeons with beriberi disappear through injections of this extract.

**Effect of adrenalin on the photographic plate (Photoaktivitätsstudien. II. Einwirkung des Suprarenins auf die photographische Platte).** Vollmer (H.), Biochem. Ztschr. (Berl.), 1926, 173, 389; Abst. Physiol. Absts., 1926, 11, 386.

One-tenth per cent adrenalin has a strong effect on photographic plates, although it does not affect potassium iodide. The photo-activity is increased by irradiation, but after long standing the photo-activity and the hypoglycemic action are lost. Old inactive adrenalin may be reactivated by irradiation. Insulin preparations increase the photo-activity, possibly due to the acid they contain. Other hormones appear not to be photo-chemically active.

**Sudden death of endocrine origin.** Bonilla (E.), La Medicina Iberia (Madrid), 1926, 434, 262-266.

Bonilla considers different theories offered in explanation of pathogenesis of sudden death of adrenal or thymic origin asserting the clinical reality of both. As regards the former he believes that the marked sensitiveness to insulin shown by Addisonians and by animals deprived of their adrenals, the constant hypoglycemia of both conditions and the resemblance between clinical adrenal death and insulin hypoglycemia indicates adrenalin deficiency as the determining factor. Thymic death he inclines to regard as due to mechanical pressure.—G. M.

**The testis and thyroid in a hen-feathered silver-grey Dorking cock.** Buchanan (Gwynneth), British J. Exper. Biol., 1926, 4, 73-80.

This paper describes a case of an apparently normal silver Dorking cock becoming hen-feathered. The testes showed large masses of "luteal" cells, encapsulated fibrosed masses, abnormal spermatogenesis and non-functioning tubules. The thyroid showed myxedematous and cystic conditions, giving the appearance of an under-functioning gland. It is suggested that such a hypothyroid condition may be a controlling factor in hen-feathering, either by acting in combination with the gonad secretion or by altering it. The thyroid and gonads are believed to act antagonistically in this —M. O. Lee.

**Pathology and physiology of milk digestion in infants.** Demuth (F.), Ergebn. d. inn. Med. u. Kinderh. (Berl.), 1926, 1, 118.

The author does not believe that he can obtain specific action by the action of organotherapeutic agents. The actions

of the various hormones upon digestion are as follows: Thyroid stimulates the gastric secretion through furthering of metabolism in the gastric epithelia, perhaps also through mobilization of chlorids. Acidity is increased by administration of thyroid extract. The effect of the thyroid hormone in Basedow's disease and in myxedema is variable. Pineal, parathyroid and thymus extracts increase gastric secretion. Suprarenal gives variable results, there being first a depression, then a stimulation of gastric secretion. The irregular absorption of suprarenal material probably plays an important part in digestion. Ovarian preparations increase while testicle preparations vary in their effect. Hypophysis extract inhibits in dogs. Pituitrin inhibits gastric secretion in adults, but in children and infants it diminishes gastric acidity at first but later increases it. Pancreatic hormone has given variable results. Some have found that injection of insulin in dogs will produce inhibition of acidity in one hour while Demuth found that in infants there is a lowering of acidity in the first two hours, followed by a longer period of increased acidity, reaching the maximum point in about nine hours.—Increased peristalsis is produced by thyroid, thymus and hypophysis.—M. B. G.

Clinic on endocrinopathies. Moehlig (R. C.), Ann. Clin. M. (Balt.), 1926, 5, 247-252.

Other factors concerned in carbohydrate metabolism have been neglected since the discovery of insulin. Pituitary diabetes is not uncommon. It is remarkably independent of the diet and does not respond to insulin as does pancreatic diabetes. The first case presented is that of a patient 50 years old whose mother died of diabetes. The patient menstruated at 14 years and stopped at the age of 16 years. About this time she developed severe migraine attacks at intervals of one to two weeks and for the last three years at intervals of three to four weeks. At 29 years she developed acromegalic features with failing vision. X-ray and perimetric examination gave evidence of pituitary disturbance. At 47 years she developed the usual symptoms of diabetes with high blood sugar and glucosuria. She did not respond to a maintenance diet and insulin. She was given posterior lobe pituitary extract and three hours later insulin. (It must be emphasized that insulin and pituitrin must not be given together as they are antagonistic.) Despite a high blood sugar she did not show glycosuria. After a few days on the pituitrin and insulin the blood sugar was still above normal but lower than previously. On pituitrin alone the blood sugar gradually reached normal and remained so for several months. She was free of her migraine attacks and symptoms of diabetes. She passed through an attack of acute gangrenous appendicitis and no reference was made to the treatment of the diabetes. About 9

months later her blood sugar again became high and she had glycosuria. She has been under treatment for 2 weeks with pituitrin alone and she has a normal blood sugar and again feels well.

Because of a close relationship of the thyroid gland to scleroderma, this second case has some bearing on the etiology of the disease. The patient developed true tetany one month after operation in conjunction with symptoms of scleroderma. She had the usual symptoms of exophthalmic goiter with basal metabolism 40 per cent above normal. Lobectomy was performed. Symptoms of scleroderma and tetany came at about the same time, one month after the operation. The Troussseau and Chvostek phenomena were present. The skin was dry. Some of the symptoms suggested myxedema. The basal metabolism was minus 24 per cent. The calcium content of the blood was 12 mgm. per 100 cc. She showed remarkable improvement on dessicated thyroid extract  $\frac{1}{2}$  grains, and calcium lactate 5 grains, t.i.d. Medication continued for 2 months. Symptoms of tetany improved, and the skin became softer and more moist. The possibility exists that the parathyroids hypertrophied, thus accounting for the improvement in the tetany symptoms. This would not explain the improvement in the scleroderma. This case showed at first marked hyperfunction of the thyroid. Following operation marked hypofunction of the thyroid is manifested by scleroderma. The last basal metabolism showed plus 6 per cent.—Author's Abstract.

**Hyperthyroidism, myxedema and diabetes.** Wilder (R. M.), Arch. Int. Med. (Chicago), 1926, 38, 736-760.

The author reports a study of 38 cases of frank diabetes combined with states of hyperthyroidism and of one case of diabetes associated with myxedema. It was found that the association of diabetes and hyperthyroidism occurs with a frequency of about 1.1 per cent of all cases of hyperthyroidism. Exophthalmic goiter is less frequently complicated by diabetes (0.6 per cent of all cases) than by adenomatous goiter with hyperthyroidism (2 per cent). The study is not concerned with alimentary glycosuria, which is a much more common phenomenon in cases of hyperthyroidism and does not represent, in the author's opinion, any actual abnormality of carbohydrate metabolism as herein defined. The symptoms of hyperthyroidism in a patient with diabetes may be obscured by those of diabetes. This is particularly true in cases with severe acidosis or diabetic coma. It is advisable, therefore, to consider the possibility of hyperthyroidism in all cases of diabetic acidosis. A mild and possibly inconspicuous diabetes may be fanned into flame by hyperthyroidism, and severe hyperthyroidism (crisis) will readily provoke coma in a diabetic patient. The requirement of insulin is increased by hyperthyroidism. Iodine, administered as compound solution in a dosage of from 20 to 60 minims daily to patients suf-

fering from combined exophthalmic goiter and diabetes, reduces the intensity of the diabetes. This effect parallels that on the basal metabolic rate. Iodine has little or no influence on the course of diabetes associated with adenomatous goiter with hyperthyroidism, and is without effect in cases of uncomplicated diabetes. Thyroidectomy is almost always followed by a considerable gain in tolerance in diabetes complicated by hyperthyroidism. Sometimes this is so great as to suggest an actual cure of diabetes, but the response to glucose test meals may still reveal the persistence of the diabetic tendency. Cure may also be simulated when a hypothyroid state is induced by the operation. A case of juvenile diabetes is cited to illustrate the palliative effect of myxedema developing in diabetes. When the basal metabolic rate of this child was restored to normal the previous diabetic state returned. Special precautions are necessary when operating on patients with diabetes complicated with hyperthyroidism. The period of exacerbated toxicity which so often follows thyroidectomy is extremely dangerous. There is also considerable danger of provoking hypoglycemia in these patients since they may be peculiarly sensitive to overdoses of insulin. Hypoglycemia coma may be differentiated from other conditions of collapse by the fact that it is usually attended by a striking elevation of the blood pressure. The phenomena exhibited by patients with diabetes combined with states of hyperthyroidism or hypothyroidism may be related to the general metabolic rate and thus may be explained without recourse to speculation as to a specific interdependence of thyroid and pancreas. It would seem that at lower metabolic rates the tissue cell is capable of utilizing a given amount of glucose with less insulin, and that with higher metabolic rates the requirement of insulin is disproportionately increased.—Author's Abstract.

**The dependence of secondary sex-characters upon testicular hormones in *Lebistes reticulatus*.** Blacher (L. J.), Biol. Bull. Marine Biol. Lab. (Woods Hole), 1926, 50, 374-381.

In six *Lebistes* males the disappearance of the male sex colors was paralleled by the atrophy of the testes. The intensiveness, shape and development of the characteristic black, red and yellow pigment spots appear to depend upon the hormones produced by the testes. The female coloration is characteristic of the asexual forms. In one hermaphrodite both testis and ovary were present and also both male and female secondary sex characters. The author concludes that the male in *Lebistes* is heterozygous (XY) and the female homozygous (XX) as to sex chromosome composition.

—M. O. Lee.

**Female sex hormone.** Frank (R. T.) & Goldberger (M. A.), J. Am. M. Ass. (Chicago), 1926, 87, 1719-1720; Abst. A. M. A.

The authors advocate the demonstration of the female sex hormone in the human blood as a clinical test applicable for the following purposes: (a) To determine the approximate time of ovulation in a given case. The time at which the hormone is first demonstrable in the circulating blood should correspond closely to the period at which the follicle reaches maturity. (b) To determine early pregnancy, especially in doubtful cases. The test becomes positive by the sixth to the eighth week of gestation. In a patient with nephritic edema, in whom bimanual examination proved inconclusive, the authors were able to diagnose the presence of gestation by means of the blood test. The sole source of error to be considered is the rare condition of persistence of the corpus luteum, with amenorrhea, in the absence of impregnation, or a test taken immediately before a delayed menstruation does occur. (c) To determine whether menorrhagia or metrorrhagia, in a given case, is due to an excess or deficiency of circulating hormone. The blood should be obtained at the onset of a period of bleeding, as after uterine bleeding has persisted the general circulation may already be depleted of its hormone content. (d) To determine the sex of persons with absence of parts of the genital tract (vagina, uterus) or pseudohermaphrodites. Here positive results alone are of value. The authors describe their technic in detail.

A study of the basal metabolism, weight and blood chemistry following bilateral oophorectomy. Geist (S. H.) & Goldberger (M. A.), Am. J. Obst. & Gyn. (St. Louis), 1926, 12, 206-217.

The authors studied the effect of castration on the basal metabolism, weight and blood chemistry, in order to determine if in human females, living under normal conditions, the removal of the gonads exerts any definable effects, and also to ascertain if possible, whether the removal of the ovaries is followed by results of sufficient physiological importance to make it advisable to conserve them when technically possible. A total of 48 cases was studied. In all of the women the menstrual function was still active before operation. Seven cases were used as controls. The patients were weighed immediately before operation after fasting 18 hours; in addition 15 cc. of blood was taken from the median basilic vein at this time for chemical analysis and the basal metabolism determined. The process was repeated two weeks after operation, and again three to five months later. There seemed to be manifested a tendency to weight increase following the operation, though the belief that castration in women is always followed by weight increase must be modified. The basal metabolism studied also showed a tendency for diminution. There was no definite relationship between the weight gain and the basal metabolism rate. The case with the greatest diminution in basal metabolism

presented no weight change. The study of the blood chemistry revealed no significant change up to a period of three months post-operative, and this same lack of variation in blood pressure was also noted. To sum up the result of investigation it would seem that castration in women with normal functioning ovaries does not result in a consistent variation in basal metabolism or the body weight; there seems to be no definite relationship between the variations between weight and basal metabolism. These results may be due to: the inaccuracy of our present method of clinical examinations; influence of other extraneous factors; the absence of any ovarian influence. These changes are not of sufficient fundamental importance to warrant their being used as an argument for the conservation of the ovaries.—Author's Abstract.

A case of "eunuchofeminismus" with Parkinsonism and psychic alterations following epidemic encephalitis. Korst (L.), Jahrb. f. Psychol. u. Neurol., 1925, 32, 57; Abst. Arch. Neurol. & Psychiat., 16, 793.

The author believes that the centers for water, sugar and temperature regulation are placed about the third ventricle: the ganglion paraopticum, the nucleus periventricularis and the tuber cinereum. Diseases of these nuclei would therefore produce diabetes insipidus or mellitus, dystrophia adiposogenitalis, acromegaly, dwarfism, etc. The case reported is that of a chauffeur, aged 21, who complained of headache, "hystero-epileptic" attacks and pain in the entire body, coming on one year after an attack of encephalitis. There was gradual increase of weight; loss of the hair of the face and body; atrophy of the testes and impotentia coeundi with retained libido; polydipsia and polyuria, without sugar in the urine; increase of fat of feminine distribution, and well developed breasts. In walking there were no movements of the upper limbs, especially the right. Muscle tonus was increased, but the reflexes were normal. There were no pathologic reflexes. The sella turcica appeared normal. Mentally the man was irritable and excitable, and he confabulated. The author separated the clinical picture into three distinct symptom complexes: (1) "Eunuchofeminism," shown by decrease in size of the gonads plus the feminine type; (2) polydipsia and subnormal temperature; (3) Parkinsonism plus psychic abnormalities. The author believes that polyuria may be hypophysial in origin as well as neurogenic, and dependent on an alteration of the ganglia paraoptica and of the tuber cinereum. The hypothermia and hyperthermia depend on alteration of the tuber cinereum. In view of the normal sella turcica, as shown by the roentgen ray, the author believes that the disease is probably near the third ventricle. To explain the case completely the author postulates disease in the striate system, as the cause of the Parkin-

sonism, the ganglion paraopticum and the tuber cinereum, and perhaps in various parts of the cortex.

**Menoform, the hormone of the oestrous cycle.** Reactivation of senile mice, antimasculine effect, effect on metabolism. Laquer (E.), Hart (P. C.) & De Jongh (S. E.), Versl. d. k. Akad. v. Wetensch. Wis-en natuurk. Afd. (Amst.), 1926, 35, 329-335; Abst. Physiol. Absts., 1926, 11, 380.

Oestrous was produced in a few senile female mice by 3 menoform injections given in the course of one day. The growth of the genital organs was inhibited in 3 male rats. In 3 series of 5 to 11 castrated female rats the gas metabolism was distinctly increased. The controls received injections of liver extract.

**Pituitrin and diuresis in man.** Adolph (E. F.) & Ericson (G.), Am. J. Physiol. (Balt.), 1927, 79, 377-387.

Pituitrin injected intramuscularly in men at the same time that various solutions were taken by mouth, did not inhibit the excretion of solutes. Pituitrin inhibited completely the extra excretion of water following ingestion of pure water, but not the extra excretion of water following the ingestion of salts in solutions more concentrated than the maximal excretory concentration. When water and salt (KCl, urea) were taken in solutions isotonic with blood plasma, the presence of pituitrin allowed the excretion of the amount of water which was required for salt diuresis, the remainder was retained. Pituitrin renders the kidneys insensitive to an excess of water in the blood plasma. This fact helps to distinguish diuretic influences due to dilution from those due to salt excretion.—Author's Abstract.

**Studies on diabetes insipidus.** Bourquin (Helen), Am. J. Physiol. (Balt.), 1927, 79, 362-375.

Diabetes insipidus was produced in numerous dogs by the cauterization of the floor of the third ventricle. Lesions other than in the mammillary bodies were ineffective. It is deduced that diabetes insipidus is an irritation rather than a deficiency phenomenon for it is produced by slight injury to the proper area but not by severe injury to or depression of that area. The diuresis must be due to a substance produced at the site of causative disturbance as a result of the irritation, which acts directly or indirectly as a diuretic; the hypophysis would not seem to be responsible for it since hypophysectomy without injury to the proper area in the floor of the third ventricle failed to produce diabetes insipidus which, however, was produced in hypophysectomized animals by injury to that area, results confirming Roussy (1925). The thirst of diabetes is secondary to the diuresis for the diuresis developed in operated animals restricted to their average pre-operative water intake and quickly produced manifestations of dessication in diabetic animals

deprived of water. Neither the autonomic nor somatic nervous systems are concerned in the diuresis for diabetes insipidus ran its typical course after transection of the spinal cord at the level of the eighth cervical vertebra, double vagotomy below the diaphragm, and paralysis of the parasympathetic nervous system with atropin. Cross transfusions between severely diabetic and normal animals performed under novocain anesthesia failed to alter the per minute volume urine output in some experiments, but caused a brief diuresis over a period of from 4 to 6 minutes in others. The latter result was never obtained in cross transfusion between normal animals.—R. G. H.

**Variations in blood pressure induced by repeated injections of extracts of posterior lobe of the pituitary gland.** Geiling (E. M. K.) & Campbell (D.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1926, **29**, 449-460.

Repeated injections in cats and dogs of a preparation of posterior lobe that had been freed from tissue depressor substances resulted sometimes in mixed pressor-depressor responses, sometimes in pure depression, depending on the species, the dose, the time interval between injections, and the rapidity of entrance into the circulation. Typical depression was more readily obtained in cats than in dogs. The authors hold that the depression in blood pressure is probably due to alteration in the cardio-vascular apparatus resulting from the first dose. This effect is believed to be an intrinsic property of the hormone and not due to the presence of depressor substances.—C. I. R.

**Prophylactic intravenous injection of pituitary extract in the third stage of labor.** Jess (F.), *Zentralbl. f. Gynäk.* (Leipz.), 1926, **50**, 2440; *Abst. J. Am. M. Ass.*, **88**, 70.

In both normal and pathologic births, Jess gives an intravenous injection (a syringeful) of a pituitary extract within five minutes after delivery: he repeats the injection if the placenta does not come away within twenty minutes. Tables covering 500 treated cases and 500 control cases show that the prophylactic injections reduced the average time from 19.9 to 9.5 minutes; the average loss of blood from 393.2 to 187.8 gm.; the number of cases in which more than 1,000 gm. of blood was lost from 28 to 10, and the number of Credé expressions from 17 to 8. The necessity for manual separation was not lessened. Placental fragments were retained in one of the treated and two of the untreated cases. A table dealing with the pathologic deliveries separately shows, in general, a corresponding improvement in the prophylactically treated cases over those in which the injections were not given.

The pituitary (posterior lobe) principle in circulating blood.  
Krogh (A.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, 29,  
177-189.

A method is described in detail for perfusing frog legs, in which the reaction of the melanophores is used as a quantitative measure of the concentration of pituitary active principle. Evidence is presented that pituitary material loses oxytocic capacity as well as "pigmentary effector" capacity in proportion to the time elapsing after death of the animal before the material is collected. This fact is taken as evidence that the two properties depend on the same substance. However the oxytocic principle is stable in solutions of pH 4.5, or less, while the "pigmentary effector" principle deteriorates after standing several days. The author's explanation is that the different effects are due to separate atomic groups within the same molecule, and that such groups can be modified chemically and made inactive without affecting the other groups. By perfusing with horse serum it was found that blood drawn from the saphenous vein contains approximately 50 per cent less hormone than that from the jugular vein. Spinal fluid contained only 25 per cent of the concentration present in jugular blood. The concentration in human blood was found to be considerably less than in horse blood. It is suggested that the normal function of the pituitary hormone is to maintain capillary tonus. Considerable amounts are destroyed by the tissues.—C. I. R.

The endocrine glands, especially pituitary, in idiocy. (Über die Beziehungen der endokrinen Drusen, insbesondere der Hypophyse, zur Idiotie.) Lazar (E.) & Weiser (W.), Trans. Second Congress for Hygienic Teaching (Heilpadagogik), (München), July-Aug., 1924.

The authors made use of the following methods of investigation: (1) Changes in the sella turcica and thymus; (2) the Abderhalden ferment reaction to determine endocrine dysfunction; (3) gas metabolism to measure hyper- and hypo-function of the pituitary and thyroid glands. Of the 140 imbeciles examined, there were only two normal and 36 almost normal sella turcicas. In the sella changes in the form and in calcareous shadows in the pituitary fossa due to the periosteal exostoses, periostitis and excrescences were seen. The dorsum sellae showed changes in shape, size and consistency because of this calcification. The authors considered that these bony changes produced a disturbance of the pituitary function. The Abderhalden test showed changes in the majority of instances, which, while not characteristic from a diagnostic viewpoint, nevertheless permitted a glance into the constitutional variations. Of 80 complete ferment investigations, in only 10 were normal findings obtained. The authors agree with Ewald that acquired constitutional changes due to endocrine abnormalities can

be confirmed by this reaction. Based upon the work of Stetten and their own investigations, they feel that they can judge the influence of endocrine glands both by clinical signs and by the Abderhalden ferment reaction. Whether or not this can be of any therapeutic value remains to be seen by further study. The gas metabolism tests showed abnormal values in nearly all of the cases.—M. B. G.

**Induction of labor by means of pituitary extract.** Scott (W. A.), Am. J. Obst. & Gyn. (St. Louis), 1926, 12, 571; Abst. J. Am. M. Ass. 88, 56.

The author reports on his efforts to ascertain how many obstetricians are using pituitary extract to induce labor, either with or without other drugs, their opinions of its value, and his own experience in several hundred cases. He concludes that there is no method of inducing labor that is absolutely free from danger to either mother or child. The induction of labor by the use of pituitary extract after castor oil and quinine is practically free from maternal danger if properly used. This method has some dangers for the child even with the best of technic, and this danger is considerably increased by improper use of the method. This danger consists for the most part of the evil results of the occasional tetanic contractions which result, but such contractions can usually be controlled by the administration of an anesthetic. There is almost unanimous opinion among those using this method that the original dosage as proposed by Watson is too large, and they either use smaller doses throughout or start with smaller doses and increase slowly. The method is being used much more extensively than one would gather from the literature, and those who have used it in a considerable number of cases are, for the most part, continuing to employ and have confidence in it.

**Hastening development of female genital system by daily homoplastic pituitary transplants.** Smith (P. E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 24, 131-132.

Homoplastic transplants were taken from full grown white rats of both sexes and transplanted to immature females. Sexual maturity was much hastened, occurring 5 to 6 days after weaning when treatment began at weaning time, instead of 80 to 100 days later. It is the anterior pituitary component which is the active agent. These changes do not occur if the ovaries are removed. Methods other than daily transplants are not effective. If this treatment is given older animals the ovaries enlarge and the follicles tend to become cystic.—J. C. D.

**The disabilities caused by hypophysectomy and their repair.** Smith (P. E.), J. Am. M. Ass. (Chicago), 1927, 88, 158-161.

A study has been made on 110 rats from 25 days to 18 months

of age. A ventral transphenoidal approach was employed after several other methods had proved impracticable. It was found that hypophysectomy produces an invariable and characteristic syndrome in the rat, the chief features of which are inhibition in growth in the young animal or a loss of weight in the mature animal; atrophy of the thyroids, suprarenal cortex and sex organs; weakness and cachexia. The animal survives for months. The disabilities arising from hypophysectomy can be nearly or completely cured by daily pituitary homotransplants. Intraperitoneal injections of saline extracts (suspensions) made from ox pituitaries prepared by the method of Evans and Long do not repair the atrophied thyroids or suprarenal cortex; and these injections not only do not repair the atrophied sex organs but prevent their repair by the pituitary transplants. Skeletal growth is stimulated by injection of the bovine fluid. A lesion of the hypothalamic region of the brain (tuber cinereum) gives rise to a syndrome which is distinct from that caused by pituitary ablation. This tuberal syndrome is characterized by extreme obesity and atrophy of the genital system; neither the thyroids nor the suprarenal cortex atrophy. In certain cases the total length of these animals may be reduced; in other cases it is unaffected.—R. G. H.

**The effects of injecting anterior hypophyseal fluid on the course of gestation in the rat.** Teel (H. M.), Am. J. Physiol. (Balt.), 1926, 79, 170-182.

The gestation of pregnant rats which are injected with anterior hypophyseal fluid from the day after they accept the male until term exhibits the following deviations from the normal: The gestation period is lengthened from 2 to 6 days. This lengthening of the gestation period has been totally accounted for in a corresponding delay in implantation: that is, implantation, which normally occurs on day 6 has been shown to occur on days 9 to 12. Term fetuses invariably die in utero, and after lying in the uterus for from 24 to 48 hours are expelled stillborn. The death of the term fetuses in utero is due to a failure of the birth mechanism of the mother. The placenta is slowly dislodged and the young die possibly of asphyxia. That the injury is not primary in the fetuses has been shown by removing them from the uterus at term and rearing them with a foster-mother. The persistence of abnormal lutein tissue, which is a specific effect of anterior hypophyseal fluid, is always associated with the failure of the birth mechanism. It is thought that the persistence of this lutein tissue is directly responsible for the inability of the mother to give normal birth to her fetuses. The average weight of term fetuses of injected animals is greater than that of normal term fetuses (6.6 grams and 5.8 grams, respectively).—Author's Abstract.

Some thoughts and experiments in relation to the hormones: the crystallization of insulin. Abel (J. J.), Proc. Inst. Med. (Chicago), 1926, 6, 108; Crystalline insulin, Abel (J. J.), Proc. Nat. Acad. Sc., 1926, 12, 132; Abst. Am. J. Dis. Child., 32, 927-928.

Commercial insulin contains 80% or more noninsulin substance. According to a previous report (Researches in Insulin: I. Is Insulin an Unstable Sulphur Compound? J. J. Abel and E. M. K. Geiling, J. Pharmacol. & Exper. Therap., 25, 423, 1925), repeated precipitation with sixth normal pyridine and redissolving with sixth normal acetic acid; grinding of the precipitate with phenol (about 90%); recovering the active part from the phenolic supernatant with ether, alcohol or water, precipitating and finally separating the insoluble portion, leaves the acetic-acid soluble, comparatively pure insulin "fraction 4." From a solution of acetic acid of this fraction, the contaminating substance was precipitated with brucine (6 gm. in 95 cc. sixth normal acetic acid) and the insulin precipitated by sixth normal pyridine. The crystals thus formed may be washed with distilled water, redissolved in acetic acid and reprecipitated as before; or they may be dissolved in fifteenth molar disodium hydrogen phosphate and then acidulated drop by drop with sixth normal acetic acid and left standing for slower precipitation which yields larger crystals. Insulin crystals are doubly refractive, of the rhombohedral division of the hexagonal system, melt sharply at 233 C., give a biuret reaction and positive Millon's, Pauly and ninhydrin tests, are soluble in dilute alkalis and acids but not in distilled water, and are easily rendered inert by boiling in tenth normal sodium carbonate (or sulphuric acid) which liberates the labile sulphur which seems to parallel quantitatively the hypoglycemic potency of the extract. As little as 0.01 mgm. per kgm. of this purified insulin lowers the blood sugar of a rabbit to approximately the convulsive level of 0.045%.

Protein requirement as determined in diabetic children. Bartlett (W. M.), Am. J. Dis. Child. (Chicago), 1926, 32, 641.

Children between the ages of 4 and 14 years maintain a positive nitrogen balance, grow in stature, gain weight at a normal rate and develop normally when supplied with 0.06 to 1.0 gm. of protein per kilogram of body weight, provided their caloric requirement is fulfilled and the diet is adequately chosen from foods rich in vitamins. The protein requirement of children bears no relationship to the fatty acid: glucose ratio, provided it is compatible with a persistent absence of ketosis. The protein requirement of children varies inversely with the age and is directly proportionate to the rate of growth. It is possible, and in certain cases of diabetes mellitus and chronic nephritis it may be advisable, to feed diets much lower in nitrogen than is usual. Provided the caloric

requirements are fulfilled, the diet is rich in vitamins and is adequately chosen from vegetable and animal sources, no evidence of protein starvation will be manifest.—M. B. G.

**Studies on diabetic lipemia. I.** Blix (G.), *Acta med. Scand. (Stockholm)*, 1926, **64**, 142-174; *Abst. Chem. Absts.*, **20**, 3737.

A study of the petroleum ether fraction from the blood of 36 normal subjects (male and female) of the ages 17 to 42 years leads to the conclusion that in women the upper limit for neutral fat is 0.05% and in males 0.09%, while for the total fraction (neutral fat-free cholesterol) the upper limits are set at 0.14 and 0.16%. Of the various circumstances affecting the blood lipemia, arteriosclerosis is sometimes found associated with an increase in free cholesterol, but this is apparently not a common symptom. Age does not seem to cause any change in the blood lipoids, nor could there be any proof of an influence of the climacterium on lipemia. In the few obese subjects examined there was variation from the normal in lipemia, though obesity of hypothyroid origin probably leads to high blood fat values. Dietary influence must, of course, be taken into consideration, but the evidence of hyperlipemia in normal fasting individuals seems uncertain. In one normal 20-year-old woman the petroleum fraction of the blood has remained remarkably constant over a period of 15 days of fasting. Experiments on 11 normal subjects receiving 0.6 to 1.4 grams of fat per kg. in the form of butter or bacon fat (in one case pure olive oil) show that the neutral fat and the free cholesterol determination for 6 hours at hourly intervals after feeding do not change uniformly. Whereas the neutral fat part of the petroleum ether fraction does increase (0.02-0.08%), the free cholesterol remains practically constant in most cases. In several experiments performed on two dogs receiving 40-50 grams of grease with their diet, besides a large amount of meat and bread (after 24 hours fasting), a steady rise in the neutral fat of the blood has been observed which reaches a maximum two to four hours after feeding, but the cholesterol remained practically constant. In one depancreatized dog the rise in neutral fat was very large and the maximum value was reached after six hours. Likewise on experiments on nine healthy, non-diabetic subjects a comparison of the blood fat in a fasting state and then three to four hours after breakfast and after dinner failed to demonstrate more than 0.02-0.03 grams variation above and below the normal lipid value per 100 cc. blood. In another group of three healthy individuals the Petrén high fat diabetic diet was tried, which produced an acidotic condition in all, but the fasting blood fat values with one exception remain within normal limits of variation, but they did show a marked post-absorptive hyperlipemia.

Studies on diabetic lipemia. II. Blix (G.), Acta med. Scand (Stockholm), 1926, 64, 175-233; Abst. Chem. Absts., 20, 3737-3738.

Earlier observations that strong hyperlipemia is a rare symptom in diabetes, while moderate and slight degrees of hyperlipemia are not uncommon, has been confirmed, a lipemia of 6.6% having been found in only 1 out of 49 cases examined. In 23 cases of diabetes the hyperlipemia did not exceed 1%. The hyperlipemia is much more common in the condition of active diabetes, and the hyperglucemia is regarded as a much more sensitive manifestation of diabetes than the hyperlipemia. In coma hyperlipemia was invariably found, but this was of very variable intensity. Likewise in cases where coma was impending there were almost always cases of hyperlipemia. Considerable post-absorptive hyperlipemia was observed only in conditions of marked acidosis; in cases of mild and slight acidosis the blood fat was frequently normal. As a rule no close parallelism exists between the blood fat and blood sugar in the individual, but when under treatment the hyperglucemia recedes there is likewise a more rapid fall in the blood fat, and when the hyperglucemia becomes exaggerated there is also a rise in the fat. The hyperlipemia is therefore not regarded as a separate manifestation but a secondary phenomenon resulting from defective carbohydrate metabolism. The rapid disappearance of hyperlipemia has been often observed in patients taking 200-250 grams of fat daily. In one instance with an initial hyperlipemia of 6-7% this became nearly normal in a week and the hyperlipemia was entirely abolished in a month on this high fat diet. In patients on the Petrén diet for four to five years there has been no sign of overstrain of the fat-oxidizing mechanism. The production or maintenance of diabetic hyperlipemia appears to be quite independent of the food fat though a diabetic may respond to a sudden increase of fat in the diet with a transient rapid rise in the blood fat, and fasting in the active diabetic condition may likewise cause a transient susceptibility to food fat. The exact mechanism of the "susceptibility" to hyperlipemia is not understood, but it may share with the susceptibility to acidosis which also varies in different diabetics. It is indeed suggested that the variable susceptibility of patients to ketonuria and to alimentary hyperlipemia may antedate the development of the disease, as the same condition is even observed in normals on a diabetic diet. The course of the hyperlipemia in most of the observed patients suggests a close dependence of the hyperlipemia on the temporary degree of the defect of the carbohydrate metabolism. In only a single instance a marked independence of hyperlipemia from the direct manifestations of the disturbed carbohydrate metabolism was noted. In insulin treatment a reduction of the hyperlipemia as well as of the other active symptoms was regularly found. As in the case of patients who do not receive the insulin treatment the reduction of the hyperlipemia

took place very rapidly in some and much more slowly in others. In two coma cases the blood fat curve following insulin has been studied carefully for a number of days, and it was found to run a course closely paralleling the oscillations of the blood sugar or blood carbon dioxide capacity curves. Only in very few instances did the insulin effect upon the blood fat last longer than on the blood sugar, and a clearly recognizable fall in the blood fat was observed in one hour.

**Studies on diabetic lipemia. III.** Blix (G.), *Acta med. Scand.* (Stockholm), 1926, **64**, 234-259; *Abst. Chem. Absts.* **20**, 3738.

The lipemia in mild and moderate cases of diabetes in patients under 50 years of age exhibits no peculiarities as compared to lipemia in the severe cases of diabetes. The active condition of diabetes may or may not bring on hyperlipemia, while in the inactive condition the blood fat of the diabetic is usually normal. In patients with mild or moderate diabetes and over 50 years of age some degree of hyperlipemia and hypercholesterolemia may exist which is independent of the active symptoms of the disease and are probably of different origin than the hyperlipemia in younger persons. A one or two-day fast is followed in most cases by a decrease of hyperlipemia, the most marked fall occurring in the early hours of the day, and even where the blood fat did rise from morning to morning the blood fat did fall during the first 12 hours of the fasting day. The rise in the blood fat curve after ingestion in mild or moderate diabetics was not generally greater than that found in normal persons on their ordinary diet, and sometimes not even as great as the rise in normal persons living on the diabetic diet, and sometimes not even as great as the rise in normal persons on their ordinary diet, and the alimentary hyperlipemia in the diabetics does not as a rule last longer than in normal individuals. There is therefore no relation between the degree of active diabetic symptoms and the magnitude of the post-absorptive rise in blood fat. Nor is there any relation between the mobility of the fat curve after fat ingestion and the level of the lipemia at the time. In a fasting condition in the morning there may be even a fall of the lipemia level after fat ingestion in spite of the initial hyperlipemia. Insulin has no effect on the post-absorptive blood fat curve in diabetics. Furthermore, when a fatty meal is repeated several times during the day the alimentary hyperlipemia becomes gradually less and may even be absent ultimately. The ingestion of bread was followed by a distinct decrease in hyperlipemia in a number of cases. While after the ingestion of meat the results were variable, the lipemia curve either rising or falling, or even remaining unchanged. The explanation generally accepted that diabetic hyperlipemia is due to a slow rate of outflow of fat

from the blood is flatly rejected. It is suggested that the diabetic hyperlipemia should be regarded as a regulative reaction, the mechanism of which, however, must be elucidated by research before any acceptable theory can be built up.

**Hyperglycemia as a Mendelian recessive character in mice.** Cam-midge (P. J.) & Howard (H. A. H.), *J. Genetics* (Cambridge), 1926, 16, 387-392; *Abst. Biol. Absts.* 1, 14.

In an investigation of the fasting blood sugar of animals the authors noticed the occurrence of wide variations in inbred types and apparent association with albinism or melanism, the former showing higher and the latter lower values than the average. Breeding experiments with mice showed that two parents with high blood sugars (116-120 mgm. %) invariably produced offspring all having high blood sugars, but that when mice with high blood sugars were crossed with others having normal blood sugars (about 85 mgm. %), all the progeny possessed normal blood sugars. Result in  $F_2$  demonstrated that high blood sugar is a simple recessive character genetically independent of albinism, for on crossing albino mice having high blood sugars with colored mice having normal blood sugars and breeding from their progeny (all colored with normal blood sugar) the second generation consisted of 7 albinos with high blood sugars, 21 albinos with normal blood sugars, 21 colored with high blood sugars, and 60 colored with normal blood sugars, in close approximation to the theoretical 1:3:3:9 ratio. The recessive nature of high blood sugar was confirmed by a back cross ratio of 45 normal to 44 high.

**Effect of insulin and of muscular exercise on protein metabolism.** Chambers (W. H.) & Milhorat (A. T.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1926, 24, 170-171.

If the dog had fasted 1 to 5 days before injection of insulin there was an increase in nitrogen excretion. If the fast had lasted 7 to 14 days there was no increase.—J. C. D.

**High carbohydrate diet and its relation to blood sugar and glycogen contents of organs.** Eisner (G.), *Ztschr. f. d. ges. exper. Med.* (Berl.), 1926, 52, 214-248.

Graphical studies of the influence of hyperglycemia on the glycogen content of the liver were made on rabbits under the influence of an unbalanced ration consisting of bran with excess sugar one day and starvation the following day. The blood sugar curve showed an extremely high and long maintained rise instead of the normal rise and duration. Glycogen storing ability disappeared while glycogenesis remained in rabbits which were not starved but overfed with sugar. On the other hand, those which were starved maintained the glycogen storing ability. Rabbits fed on a regular

diet with added excess sugar showed a low hyperglycemic curve; it rose little if at all. Thus glycogen can accumulate in the liver. Glycogen occurrence in organs and hyperglycemia curves are hereby correlated. These findings give us an insight into the intermediary carbohydrate metabolism.—Author's Abstract.

**Insulin in malnutrition.** Fisher (L.) & Rogatz (J. L.), Am. J. Dis. Child. (Chicago), 1926, 31, 362.

Based upon observations of 27 malnourished infants who were given insulin. Of these, 17 (63%) showed increase in weight and improved nutrition, 5 gave indifferent results, and 1 died. The insulin was given intravenously or by hypodermoclysis in repeated small doses with no change in diet. Insulin, if administered in properly chosen cases of malnutrition in infancy, has been in the hands of the authors an effective if not an absolute remedy and deserves a trial when all other methods of feeding and management have failed. They advocate intravenous injection in cases of atrophy with acute toxicosis, intraperitoneal injection in atrophy without acute toxicosis and subcutaneous injection in dystrophy with stationary weight.—M. B. G.

**Insulin by mouth.** Fornet (W.), Wien. klin. Wchnschr., 1926, 39, 1109; Abst. J. Am. M. Ass. 87, 2040.

Fornet mixes insulin with bile and administers it by mouth. It does not cause sudden hypoglycemia in diabetes, but he believes that it increases the sugar tolerance. In healthy subjects it produces three symptoms peculiar to insulin, the same as if it were injected; the urine rotates polarized light to the left; the subject gains in weight, and sudden discontinuing of the administration of the hormone causes glycosuria.

**The utilization of protein, carbohydrate and fat in hypoglycemia in diabetes requiring insulin.** Gibson (R. B.), Greer (Lillian) & Barer (Adelaide), Am. J. Physiol. (Balt.), 1926, 76, 188.

In hypoglycemia there is increased utilization of fat. Sugar metabolism is augmented at high glycemic levels, fat metabolism at low levels. Total metabolism is augmented in the latter condition, the hypoglycemia being incidental to metabolic changes. Pre-operative administration of insulin and glucose shifts acid-base balance to alkaline side, which effect persists after long anaesthesia and is explained as due to binding of phosphoric acid.—C. I. R.

**The best method of insulin distribution in the management of diabetes in children (Die optimale Insulin Verteilung in der Behandlung des kindlichen Diabetes mellitus).** Priesel (R.) & Wagner (R.), Klin. Wchnschr. (Berl.), 1926, 5, 301-302.

In their first paper the authors advocated two injections at intervals of twelve hours, before breakfast and supper. They now advise in severe cases three injections of insulin, given morning, noon and night. In treating a severe case they found that even this had no effect. On further investigation it was found that the urine sugar was highest between 5 and 8 a. m., with very little blood sugar by 8 a. m. By giving the first injection at 5 a. m. before the rise instead of at 8 a. m. after the rise, there was a reduction in the urinary and blood sugar. The child improved after this.—M. B. G.

The best method of insulin distribution in the management of diabetes in children (Die optimale Insulin Verteilung in der Behandlung des kindlichen Diabetes mellitus). Priesel (R.) & Wagner (R.), Klin. Wchnschr. (Berl.), 1926, 5, 10-14.

Sugar excretion curves in hourly investigations show in insulin treated and in insulin free diabetes, a rise in the morning with a gradual drop toward noon. Three hour observations show that the influence of a rich carbohydrate diet at breakfast is more pronounced than a similar one at noon. The best method of administration of insulin is in 12-hour intervals with a larger first dose. Because of the greater sugar excretion in the morning, it is best to give the morning injection at 7 or 8 a. m. In very severe cases the daily amount is best distributed in three doses with six-hour intervals. The midnight dose advocated by some American authorities is not to be recommended, because it disturbs the night's rest. A large dose in mid-day is not as efficacious as several small doses. These rules hold only for the best insulin preparations and other rules must be made for less potent ones. The assimilation of carbohydrate and the anti-diabetic action of insulin reach the optimal point depending upon how near the blood sugar is to the normal limits.—M. B. G.

The pathology and therapy of diabetes in children (Die Pathologie und Therapie der kindlichen Zuckerkrankheit). Priesel (R.) & Wagner (R.), Ergebn. d. inn. Med. u. Kinderh. (Berl.), 1926, 30, 536-730.

This is a monograph on a timely subject by two authorities based upon their observations at the University of Vienna, Pediatric Department, in addition to a thorough review of the literature. American authors are freely quoted and acknowledgement made of work which has recently been done in America, especially by E. P. Joslin and A. F. Hartmann. The following is the subject matter of the chapters: The etiology of childhood diabetes, including the question of heredity, age distribution, grouping and constitution. The clinical consideration of the symptomatology, including

diabetic coma. Carbohydrate metabolism, acetone and fat metabolism. Blood sugar curves with a discussion of the form in which sugar circulates. Management of diabetes in infants and children, both dietary and by insulin, including diets in detail for diabetic children, based upon Pirquet's Nem system measurements. This is a very important chapter and is handled expertly. The influence of infection on diabetes, insulin resistance and the treatment with insulin are given in detail. The treatment of coma, hypoglycemia and the application of insulin, as well as foreign protein sensitization are next, and finally there is the course and prognosis of diabetes in children. An exhaustive biography, numerous charts and ninety-six illustrations are appended.—M. B. G.

**Glycosuria of the new-born treated with insulin.** Ramsey (W. R.), Am. J. Dis. Child (Chicago), 1926, 32, 790.

A boy, full term, normal delivery, 2200 gram at birth, with a family history of diabetes, was placed on complementary feeding because of loss of weight. He was admitted to the hospital at the age of four weeks and three days, with the following symptoms: Continued loss of weight, polyuria, glycosuria, thirst and profuse perspiration. After the administration of 0.5 units of insulin every three hours before each feeding, the urine became sugar free and the weight began to increase. From then on he was found to have a low sugar tolerance with a blood sugar 0.225 to 0.263. Under treatment his tolerance was raised to 4.5 per cent carbohydrates in addition to 1000 cc. of whole lactic acid milk, at the age of 5 months. He was still sugar free at the age of 7 months.

—M. B. G.

**The pathogenesis of nutritional disturbances in infants. VIII. Experimental dehydration and carbohydrate metabolism (Zur Pathogenese der Ernährungsstörungen beim Saugling. Experimentelle Exsikkose und Kohlenhydratstoffwechsel).** Schiff (E.) & Choremis (E.), Jahrb. f. Kinderh. (Leipz.), 1926, 64, 42-79.

Experimental dehydration produces diminution in glycogen content of liver and fat increase; if continued, liver sets up a fat infiltration. Rich protein feeding with dehydration produces low glycogen content in liver but high blood sugar. Blood sugar regulation is changed in hunger depending on amount of water content in child. The estimation of inorganic phosphorus in blood shows that this change is due to processes occurring in the intermediate stages of carbohydrate metabolism. Hunger hypoglycemia in infants is analogous to insulin hypoglycemia with the exception of the amount of inorganic phosphorus in the blood. Hunger in older children and in adults is not followed by hypoglycemia immediately; in older children this occurs on the third to sixth hunger day. The prompt ketonuria after twenty-four hour hunger with dehy-

dration, the absence of hypoglycemia, the increase of phosphorus in the blood, the characteristics of the blood sugar curve speak for disturbances of the pancreatic hormone. This with acidosis, relative or at times absolute hyperglycemia, are all analogous to diabetic symptoms. One can speak of dehydration as being a pseudo-diabetic disturbance of the carbohydrate metabolism. With alkalo-sis there is a disturbance in carbohydrate metabolism. Ketonuria and acidosis are used interchangeably by some but they have no relationship. Ketonuria can appear with either acidosis or alkalosis; it is only a sign of disturbed carbohydrate metabolism.

—M. B. G.

**Carbohydrate metabolism of infants with diarrhea, infections and acute intestinal intoxication.** Tisdall (F. F.), Drake (T. C. H.) & Brown (A.), Am. J. Dis. Child. (Chicago), 1925, **30**, 836.

Infants with toxicosis, infections and fever were injected with insulin and glucose either subcutaneously or intravenously. The authors concluded that glucose injected into children with these conditions is not removed as rapidly as in normal infants. In these conditions there is a derangement of the carbohydrate metabolism but this disturbance is not associated with a primary insulin deficiency. The administration of insulin in these cases did not show any therapeutic influence. No positive evidence has been obtained that insulin per se when administered with carbohydrate to malnourished infants produces any beneficial results. The action of insulin is definitely hindered by the presence of fever or infection. In infants who have died of toxemia there is usually a large amount of fat in the liver and very little glycogen. The presence of glycogen helps protect the organism against toxemia so that there is definite rationale for the administration of glucose (carbohydrate) in toxemic conditions.—M. B. G.

**Concerning the relation of guanidine to parathyroid tetany.** Collip (J. B.) & Clark (E. P.), J. Biol. Chem. (N. Y.), 1926, **67**, 679-687.

The curves for urea and non-protein nitrogen have been determined in dogs treated with various guanidine salts. These curves are contrasted with similar ones obtained in dogs submitted to parathyroidectomy. The results are interpreted as opposed to the guanidine theory of parathyroid tetany.—Author's Abstract.

**The effect of bleeding upon the serum calcium of thyroparathyroidectomized dogs.** Swingle (W. W.) & Wenner (W. F.), Am. J. Physiol. (Balt.), 1926, **73**, 372-377.

Withdrawal of considerable quantities of blood from dogs suffering from parathyroid tetany promptly relieves the symptoms temporarily, and induces a marked rise in the level of the serum

calcium. The abatement of symptoms coincides with the rise in serum calcium. Within ten or twelve hours after bleeding the calcium content of the blood again decreases and tetany again becomes manifest. Continued bleeding does not induce further increase in the serum calcium. The remission of tetany symptoms which follows bleeding cannot be considered good evidence that such procedure diminishes the concentration of a toxic substance in the circulating blood. Heretofore this fact has constituted one of the main props of the toxin theory of tetany.—Author's Abstract.

**The histogenesis of the thymus as shown by tissue cultures, transplantation and regeneration.** Popoff (N. W.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, 24, 148-151.

The author used rabbits. He studied the growth of the thymus by means of tissue cultures and by transplants. The epithelium gives rise to the reticulum but the lymphocytes infiltrate from outside or arise from connective tissue, which has invaded the gland.—J. C. D.

**Effects of thyroxin on the gaseous exchange of the white rat.** Arnoldi (W.), Ztschr. f. d. ges. exper. Med. (Berl.), 1926, 52, 249-259.

The author describes and illustrates an open system of gas analysis and tabulates findings of oxygen consumption after injection of thyroxin subcutaneously. In doses .02 mgm. per kgm. of animal augmentation of oxygen consumption is not constant. Augmentation is observed after injection of 0.4 mgm. per kgm. Injection of 0.5 mgm. per kgm. produces a rise lasting for 4 hours; this rise then falls till the twelfth hour and again rises on the seventeenth hour and stays up till the nineteenth hour. In these animals an augmentation in the oxygen consumption is also observed between the fifth and eighth day following injection of thyroxin. It is yet to be tested whether injection of diluent without thyroxin would produce such changes. If the augmentation of oxygen consumption lies within the limits of spontaneous changes, only a typical course of changes is deciding.—Author's Abstract.

**Cardiac disturbances in Basedow's disease (Les troubles cardiaques chez les Basedowiens).** Bickel (G.), Schweiz. Med. Wchnschr. (Basel), 1926, 11, 251-257.

This valuable paper is based upon a study of 80 hospitalized patients and includes a survey of the literature of representative writers. Cardiac derangements in exophthalmic goiter patients go through the same phases of evolution as cases of primary heart disease, varying from mild functional disturbances to the grave car-

diac disorders. The first or incipient phase of the syndrome is characterized by a heart rate of 100 to 150 per minute, varying with emotions, fatigue, menstruation, and infections. These variations are regarded as pathognomonic. A combination of vagotonia and sympatheticotonia in practically every patient is constant, resulting in amphotonia (Danielopolu). A predominance of vagotonia in exceptional cases explains the paradoxical instance in which bradycardia is observed. Palpitation, precordial distress and discomfort are complained of in the incipient stage. The systolic impulse is exaggerated and is often accompanied by presystolic vibration. There may be a duplication of the second sound. In about 50% of cases an inorganic murmur, systolic in time, located over almost any part of the precordium is noted. Occasionally this is heard over all the cardiac orifices, but without the definite transmissions observed in primary valvular lesions. Rarely there is observed in the second left intercostal space a distant friction sound, the interpretation of which is still doubtful. Auscultation and fluoroscopic examination reveal a slight increase in size of the heart. The cervical and other vessels throb in a manner resembling the findings in aortic insufficiency; the radial pulse, on the other hand, evinces a weakness in volume (dissociation of the cardio-radial impulsion.—Oddo). Often the pulse is bounding. Capillary pulsation is likewise characteristic. The arterial tension may be increased, normal, or diminished, varying with the type of the illness and the stage of the disease. The increase during the incipient stage of the disease is attributed by Adler and Krauss to hyperadrenalemia. Instead of the adrenalin, pilocarpin, eserine, and atropin tests which are impractical to the general practitioner, the author suggests the ocular-cardiac test, which reveals the vagus excitability, and the orthostatic test, indicating the tonus of the sympathetic nervous system. The former, practiced in a gentle, sustained manner, gives a positive result as a rule, the pulse rate often falling from 150 to 100 or lower. An inverse reflex may result from painful pressure on the eyeballs by the observer. The orthostatic test consists in having the patient quickly change from the recumbent to the standing position, when the heart rate is markedly increased. From these tests one may form a general idea of the excitability of the excellerators and inhibitors of the heart.

The second or intermediary phase is that of profound thyroid intoxication. Cardiac disturbances may here be divided into five types: (a) Simple tachycardia, often exceeding 150 per minute; (b) paroxysms of tachycardia with a rate of 170 to 180; (c) very exceptionally, the intensification of heart rapidity assumes the picture of true paroxysmal tachycardia, recognized by its suddenness of occurrence and disappearance, with a rate of 200 or more per minute (Bickel, Dill, Bamberger, Granet, and Oddo); (d) pure

extra-systolic arrhythmia, which is infrequently observed; (e) complete arrhythmia (fibrillation, flutter, or fibrillo-flutter of auricles) commonly seen. This may occur paroxysmally, intermittently, or permanently, and may lead to a fatal termination. Fibrillation and flutter must not be confused with paroxysmal tachycardia, and may continue for weeks, months, or years. The patient may adapt himself to the condition and become relatively comfortable. The heart is increased in all diameters, becoming globular in shape; the sounds become less intense, and the blood pressure is relatively lower, indicating a tendency toward decompensation.

The third clinical type is the phase of confirmed cardiac failure. This is announced by a systolic apical murmur of dilatation in association with the emaciation and asthenia incident to the disease. Auscultation reveals almost constant arrhythmia with the tachycardia still evident. Cardiac asthma or edema of the lungs may supervene. Right ventricular insufficiency is much more frequent, rarely resulting in pulmonary stasis and congestion of the renal and hepatic structures and anasarca. Despite the fact that these patients appear to be moribund, it is interesting to note that occasionally there is marked regression of all the other signs and symptoms of Basedow's disease. Circulatory insufficiency from cardiac failure results in a devascularization of the thyroid similar to that produced by surgical ligation, with reduction in size of the organ.

Heart failure is no doubt the usual cause of death in Basedow's disease. Death may occur suddenly, either directly from heart failure, or from operative intervention, during which the anesthetic may play a determining rôle.

The pathologic anatomy of the heart in Basedow's disease consists essentially in an increase of the volume of the organ. Microscopically there are observed degenerative changes in the muscular fibers with fatty infiltration, and inflammatory islets interstitially and perivascularly located, consisting especially of lymphocytes. Disseminated necrosis is likewise occasionally seen.

The toxic theory in explanation of the cardiac phenomena occurring in Basedow's disease is the most acceptable. This is associated with an intervention of the cardio-regulator nerves which indeed play the most important rôle and is largely the cause of myocardial hypertrophy. The tachycardia is especially due to an abbreviation of the diastolic periods, as a result of which the filling of the chambers of the heart becomes defective. The auricle remedies this by a more vigorous contraction, not without speedy fatigue. The work of the left ventricle is increased by the augmentation of peripheral demands. Because of the extreme increase of basal metabolism, most of the organs of the body require a marked increase of blood supply and drainage. The thyroid itself

in Basedow's disease requires five to six times more blood than the normal organ. Thus there results a deviation from habitual paths of a great quantity of blood directed toward the thyroid and head, which in serious cases amounts to more than a liter per minute. The loss of blood from elsewhere is incapable of being compensated, and is at the price of serious overdriving of the left ventricle. Through the slow, progressive intoxication of the nervous regulators of the heart, the vago-sympathetic mechanism is capable of producing sudden death. The direct intoxication of the myocardial structures through toxins in the blood is a supplemental factor lending itself toward the totality of results.

The prognosis in serious cardiac difficulties associated with Basedow's disease is much less grave than in primary cardiac conditions, for we frequently observe complete cure in patients whose hearts appear absolutely incurable. On the other hand, it is often infinitely more grave, for one frequently sees a sudden termination in patients in whom the cardiac perturbations were apparently benign. The Basedowian heart conditions require less consideration than the primary intoxication. It could be stated that cure of the Basedow syndrome is generally followed by cure of the cardiac status, the exceptions being instances in which the myocardium is independently or sequentially badly degenerated.

Treatment concerns itself with the management of the thyrotoxicosis. Direct treatment of the heart itself is of secondary importance. During the period of tachycardia with marked subjective complaints, such sedatives as valerian are useful. Arrhythmia may require eserine or quinidine. During the period of confirmed arrhythmia, quinine and quinidine counteract fibrillation and flutter. In arrhythmia with signs of decompensation, digitalis is indispensable. In partial heart block of the bundle of His, digitalis may calm the ventricular excitement. Quinidine may be employed combined or alternating with digitalis. Ouabain may also be considered in this connection. The author believes that the condition of the circulatory system is of greater prognostic value and is a more important factor in the determination of treatment than are basal metabolic studies. Moreover, he emphasizes the importance of the judicious management of the Basedowian syndrome itself as a final cure of the resultant cardiopathy.—I. B.

**Roentgenotherapy in exophthalmic goiter.** Borak (J.), Strahlentherapie (Berl.), 1926, 23, 519; Abst. J. Am. M. Ass. 87, 2134.

In early acute cases Borak irradiates the entire thyroid and the region of the thymus with 2 to 4 Holzknecht units, depending on the severity of the condition, using a 4 mm. aluminum filter. This dose is repeated at intervals of 4 to 8 days, followed by a rest of 3 to 4 weeks. Acute cases are usually more or less improved.

after one such treatment, but chronic cases do not show improvement until after 2 or 3 series of treatments. In the second and third treatment in each series the thyroid alone is irradiated, the surface being divided into zones. Each zone is treated separately, but indirectly the whole gland receives some irradiation. He gives only 4 series. An operation is suggested, if results are not seen 4 months after the beginning of the treatment. An average of 80 per cent of his cases improved in from 1 to 4 months, and about a third subsequently became free from symptoms.

**Cretinism and myxedema produced experimentally in swine.** Caylor (H. D.) & Schlotthauer (C. F.), Am. J. Physiol. (Balt.), 1926, 79, 141-148.

Swine are very satisfactory animals for the production of experimental cretinism and myxedema, because of their peculiar anatomy and physiology. They respond quickly to thyroid deficiency with definite symptoms. Distinct parathyroid glands were not found in swine, but islands of parathyroid tissue were demonstrated in accessory thyroid glands. Parathyroid tetany did not develop in swine following complete thyroidectomy. The age at which thyroidectomy was performed was of importance. The animals which were operated on before puberty showed a more marked reaction. Swine from which the thyroid had been removed apparently were hypersusceptible to disease.—Author's Abstract.

**A contribution to the iodine treatment of goiter in children (Ein Beitrag zur Kröpfbehandlung mit Jod bei Kindern).** Heid, München. med. Wchnschr., 1926, 7, 287-288.

The author found goiter almost universally present in children of 38 schools in the district of Heppenheim. Everyone in the schools, including teachers, irrespective of whether goiter was present, was given iodine tablets largely in the form "Dijodyl," each dose corresponding to 0.006 gms. of iodine. Very satisfactory results were obtained, as a consequence of which this treatment has become so popular that in some districts the entire population is taking prophylactic treatment. It is suggested that where goiter is endemic, the children, especially of pre-school age, should be given small doses of iodine for two months twice yearly.—I. R.

**Pathogenesis of sporadic cretinism.** Herrman (C.), Tr. Am. Pediat. Soc., 1926; Am. J. Dis. Child. (Chicago), 1926, 32, 782-783.

The symptoms of Sporadic cretinism are not due solely to hypothyroidism; other members of the endocrine system, more especially the anterior lobe of the pituitary gland, are probably involved. As Biedl says, the thyroid gland, if not the conductor, is at least the first violin of the secretory concert. The absence of thyroid

secretion probably impairs the function of the pituitary gland. In some mammals, the removal of the anterior lobe of the pituitary gland causes a retardation of skeletal growth similar to that caused by thyroidectomy. In tadpoles, thyroid feeding causes a rapid metamorphosis, unassociated with any increase in size. According to the latest view (Kendall), the thyroid secretion acts as a catalytic substance, and stimulates chemical changes in all the cells of the body. The increased metabolism results in metamorphosis. In sporadic cretinism the absence of this stimulation causes delayed metamorphosis which manifests itself in retardation of skeletal growth, dentition, closure of fontanelles and sutures, and the umbilical ring. Disturbances of thyroid function, as shown by enlargement, are common even in regions (supposedly) free from endemic goiter. The enlarged thyroid gland, being visible and palpable, is not easily overlooked; hypothyroidism is not so easily detected. There are individual differences in the functional efficiency of the thyroid gland. Inefficiency may not be evident until an extra demand is made on it by infection, toxemia or psychic trauma. Such a congenital inferiority is analogous to Gowers' abiotrophy, a defect in vital endurance. Heredity plays an important part in the disturbances of the thyroid gland. Several subjects in one family may be affected. Such disturbances may be of a different character in each, and the tendency may manifest itself in disturbances of other members of the endocrine system. In cases of sporadic cretinism the family history may show little evidence of disturbances of the endocrine system, because, previous to 1890, the successful treatment of hypothyroidism with thyroid extract was unknown, so that these patients were sterile; defective embryos fail to mature, or if they mature may be stillborn or die shortly after birth; the functional inefficiency of an endocrine gland may not manifest itself until late in life, so that patients who die young may show no definite signs of such inferiority. Endemic and sporadic are relative terms. Enlarged thyroid glands are not uncommon in regions (supposedly) free from goiter. There are no pathognomonic symptoms which serve to differentiate between endemic and sporadic cretinism. Those which are usually given are not sufficient. It seems probable that in districts in which cretinism is endemic, besides injurious unsanitary local conditions, which put an extra burden on the thyroid gland, there is an inferior degenerated stock. Villages situated in mountainous districts were segregated until recently. Hypothyroid subjects, being inferior, less ambitious and adventurous, would remain at home, and as their choice would be restricted, intermarriage would be common. This would favor the appearance of unfavorable recessive factors. In this respect con-

sanguinity would be a contributing cause. If subjects carrying these unfavorable recessive factors migrated to other countries, some of their children might be hypothyroid, and would be considered cases of sporadic cretinism.

**Cretinism.** Follow up report of eight cases. Kerley (G. G.), Arch. Pediat. (N. Y.), 1926, 43, 94.

These patients were followed up for periods from a few weeks to twenty-six years in some instances. It was found that they showed improvement in the physical direction but never reached their physical age mentally. They could be trained to do manual labor, a little elementary reading, but not arithmetical problems. In cases of complete absence of the thyroid gland, organotherapy in the form of thyroid extract had to be administered continually. Discontinuance of the extract was followed by retrogression.

—M. B. G.

**Myxedematous ascites removed by thyroid extract.** Marsh (H. E.), Am. J. M. Sc. (Phila.), 1926, 172, 585-588.

A woman, 37 years of age, came for examination February, 1924, for an enlargement of the abdomen. Previous to the onset of this she had noticed swelling of her hands, feet and jaw, and her skin had assumed a yellowish pallor. She had begun to slow down physically and complained of her hands and feet being cold. Her menstrual period ceased two months before coming for examination. Her appearance suggested late pernicious anemia or nephritis. The face and mucous membrane were pale, the tongue thick and beefy, the skin dry, and the abdomen was protuberant and symmetrical with a distinct fluid wave. The blood pressure was 118-80, pulse 88. Hemoglobin 55%, erythrocytes 4,290,000, leukocytes 8200, and differential count normal. An exploration of the abdomen was negative except for three gallons of yellowish fluid which was removed. The ascites gradually reformed. A basal metabolic rate was then made which was minus 37%. Following the administration of thyroxin improvement was noticeable within a few days. Her mentality, which had been sluggish, became more alert, her skin began to scale and for the first time in months she felt warm and perspired slightly. Her systolic blood pressure rose to 140 and her basal metabolic rate to minus 14 two weeks after the first thyroxin administration. A month later the basal metabolic rate was plus 7. She was then given 2 gr. of thyroid extract three times a day. The ascites entirely disappeared and the edema of the face, hands and feet cleared up. The middle of April she menstruated for the first time. Since that time she

has been taking 2 gr. of thyroid extract twice daily and has remained in perfect health.—Author's Abstract.

**Observations on the heart in myxedema.** Means (J. H.), Boston M. & S. J., 1926, 195, 455.

Two cases of cardiac complications in myxedema are reported, the first a woman with cardiac dilatation in myxedema. This case appears to be similar to those published by Zondek and by Fahr. It is pointed out that the condition is not common in myxedema. The second patient was a man with myxedema who developed anginal pain when the dose of thyroid was increased. There seemed to be a definite relationship between the amount of the drug and the amount of angina pectoris. With no thyroid the patient is myxedematous and free from angina; when sufficient thyroid is given to raise his metabolism to a normal plane he has angina. It was thought that increased blood flow is responsible. It is concluded that the discovery of any cardiac disturbance in myxedema is direct indication for very gradual thyroidization. With patients who under thyroid medication develop toxic cardiac symptoms of any sort, one must be content with maintenance at a metabolic level below that at which the toxic symptoms occur.—Author's Abstract.

**Growth and goiter (Wachstum und Kropf).** Pflüger, München. med. Wehnschr., 1926, 14, 566-568.

The stunted growth in hypothyroidism and the augmentation in height in youths with Basedow's disease would seem to lend support to the view that during the growing period of life simple goiter retards physical and mental development. Hunziker is quoted as having observed among Swiss recruits that the average stature was smaller in direct proportion with the increased size of goiter; thus he assumed that goiter retards growth. There are, however, other factors in the mountainous valleys of Switzerland which might retard growth, among which are mal- and sub-nutrition, overexertion, cretinism, inbreeding, lack of sunshine, and racial peculiarities. Indeed, it is observed that the Swiss people are generally small, even in the absence of goiter. In a subsequent study among goitrous school children, Hunziker discovered, to his astonishment, that between the ages of 7 and 16 there was no retardation, but rather an augmentation of physical and mental growth. Other observers, eminently Schiötz in Norway and Schlesinger in Strassburg, came to the same conclusions. In 1925, in a study of the relation of growth to goiter in endemic goiter regions in Baden (cretinism was disregarded), the author paid special attention to parenchymatous thyroid enlargement. He measured 9540 school children vary-

ing in age between 7 and 20 years, and concluded that in endemic regions adolescents with large thyroids show no retardation in growth. Pflüger further concludes that enlarged thyroids among adolescents in endemic goiter districts are associated with a degree of hyperthyroidism.—I. B.

**Discussion on the diagnosis of malignant diseases of the thyroid gland.** Proc. Roy. Soc. Med. (Lond.), 1925, 18, 25-40.

In this discussion Mr. James Berry, Dr. Scott Williamson, Mr. Wilfred Trotter, Mr. A. J. Walton and Mr. T. P. Dunhill were the participants. Berry stated that an early diagnosis of malignant disease of the thyroid gland is difficult. The rarity of the disease, the proneness to regard all thyroid swellings as of simple nature, and the fact that malignancy is not obviously tangible until advanced, all make for a belated diagnosis in which the glandular capsule is already penetrated. The mass in definite malignancy of the thyroid, though still following the movements of deglutition, cannot be moved upon the trachea, as innocent goiters, unless inflamed, usually can. Paralysis of the vocal cords, dysphagia, wide distribution and induration of the mass, the occurrence of hard irregular masses within the goiter, are valuable aids in diagnosis. Small tensely filled cysts within a goiter of areas of fibrosis and calcification, are innocent but apt to lead to a suspicion of malignancy. Hemorrhage into or around a goiter, with associated rapid swelling, pain or pressure symptoms, may simulate malignancy, but usually occurs in cystic goiters and adenomata. Trotter called attention to the need of discriminating between carcinoma of the cervical esophagus and malignant disease of the thyroid. This is due to the fact that paralysis of the vocal cords and swelling of the thyroid are commonly secondary to carcinoma of the esophagus.

—I. B.

**Symptom complex resembling hyperthyroidism without increased metabolism.** Strouse (S.) & Binswanger (H. F.), J. Am. M. Ass. (Chicago), 1927, 88, 161-164; Abst. A. M. A.

The authors analyze thirty-two cases which presented the symptom complex closely resembling so-called hyperthyroidism without changes in the basal metabolic rate. This complex has been known for some time under various names, but except for one report made during the course of this study, these patients have not been treated with iodine. The authors believe the results of such treatment justify the opinion that the symptoms and signs of this complex are associated with iodine deficiency. Iodine medication relieved

the symptoms but did not affect the basal metabolic rate. The suggestion is offered that the condition may be one of disturbed thyroid function. Probably it does not represent a true primary clinical entity, but it may be a secondary functional manifestation of disease processes elsewhere in the body.

**The syndrome of thyrotoxicosis and its reaction through the administration of small doses of iodine (Das Thyrotovikosesyndrom und seine Reaktion bei kleinen Joddosen).** Walberg (J.), From the Medical Polyclinic of the University of Helsingfors in the service of Dr. R. Ehrström. (Helsingfors, 1926, 148.)

This is an excellent presentation of the subject based upon the study of a series of 20 cases, along with deductions from the work of many other observers. Under the abstract consideration of the subject the author employs the term thyrotoxicosis as including the group of conditions beginning with a clearly defined Basedow's disease, down through the "Basedowoids," the "forme fruste," and toxic adenomata, to those conditions bordering on a symptomatology corresponding to the simple neuroses. The syndrome of thyrotoxicosis centralizes itself primarily in a disturbed thyroid function which is revealed by altered basal metabolism, alimentary glycosuria, and blood pressure changes. The variability in types of thyroid hyperfunction is due to the fact that no symptom is decidedly pathognomonic and clear cut; all symptoms may appear in varying combinations and degrees of severity. In the series of cases studied the results of the administration of small doses of iodine were observed. Sensitivity to iodine by these patients manifested itself in the following ways: 1. A primary improvement (the iodine remission), the promptness of which is in direct proportion to the thyroid toxicity. The remission is of general nature, including a decided drop in the basal metabolic rate and pulse rate, recession of the exophthalmos, and cessation of diarrhea. 2. Following this there is a secondary recurrence of all symptoms during treatment, the severity of the clinical picture being in direct proportion to the severity of the primary toxicity. Indeed, this return of symptoms may in the severer cases become graver than it was before the beginning of iodine administration. 3. When iodine administration is interrupted, there is likewise a marked recurrence of symptoms due to the rapidly rising toxicity. This becomes worse, reaching a clinical picture far graver than existed before the administration of iodine. The author concludes that iodine administration in thyrotoxicosis is merely a palliative procedure. The only rational use of iodine appears to be in connection with the preoperative prepara-

tion of these patients. A warning is sounded against the use of iodine in thyrotoxicosis as a curative agent, especially in the severe forms of the disease.—I. B.

**Narcolepsy—a symptom complex.** Weech (A. A.), Am. J. Dis. Child. (Chicago), 1926, 32, 672.

A case report is given of a girl, aged seven years, with a symptom complex corresponding to narcolepsy as described by Gelineau. This patient improved markedly on thyroid extract. The term emotional asthenia is suggested to describe the sudden attacks of weakness which narcoleptic patients may experience following excitement. Some of the cases may be classified as symptomatic narcolepsy where the emotional asthenia is absent. One child, eleven years of age, belonging to the latter group of symptomatic narcolepsy, did not improve on thyroid extract. The author suggests that narcolepsy is a symptom complex depending on injury of a localized brain area and is not a clinical entity of a special disease.—M. B. G.

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